DIABETESCLOSEUP

The Leading Source of Diabetes Business News

Invasion of the Cardiologists **June-July 2008 • No. 81**

From the Editor

Perhaps it was the bright California sunlight that streamed into the main hallway from the Yerba Buena gardens outside, or the simple joy of welcoming my friends in the diabetes world to my home city of San Francisco. Whatever it was, in my mind this was the best ADA Scientific Sessions in ages. Now that the dust has settled, we're pleased to bring you our annual ADA Download.

Although this ADA was a bit lighter on the device side than in previous years, heaps of new drug data more than made up the difference – and anyway, on the device side, we certainly witnessed big-time continued momentum for diabetes technology, especially CGM. On the drug side, our hands were full: pioglitazone in prediabetes, Symlin as a replacement for mealtime insulin; phase 3 data for Amylin's exenatide once-weekly, Takeda's alogliptin, Novo Nordisk's liraglutide, BMS/AZ's saxagliptin, and AtheroGenic's AGI-1067; phase 2 data for Vivus's Qnexa, BMS/AZ's dapagliflozin, Roche's R1583 (taspoglutide), Intekrin's INT131, and Sanofi's AVE0010; as well as information about a number of exciting new drug classes. Phew, it was a busy week. Look for a recap of this data in DCU Company Watch.

During the ADA, we also conducted a survey of more than 150 health care professionals and enthusiasm for CGM and incretins underscored. Specifically, a whopping 75% of health care providers surveyed expect to use more CGM in the next year, 66% expect to prescribe more Januvia/Janumet, and 58% expect to prescribe more Byetta. We published these and other key survey results in Closer Look, our real-time news service – please contact us if you don't receive this and are interested in doing so.

The 68th Scientific Sessions of the ADA will probably be remembered most for the three landmark trials that were presented: ADVANCE, ACCORD, and the VADT. Huge kudos to the ADA planning committee for fitting all three related trials into the meeting, as the interpretation of each of the three trials relies heavily on the results from the other two. The most important takeaway in our view, after listening to the experts, is that for type 2 diabetes the strategy used to lower blood sugar is <u>just</u> as important as the absolute change in A1c. Unfortunately, in many cases the message to the public is that intensive glucose control is not beneficial and may be dangerous (note the June 7, 2008, New York Times article titled "Tight Rein on Blood Glucose Has No Heart Benefits" as an example). The essential disclaimers – that the results apply only to patients with a long duration of type 2 diabetes at high risk for or with underlying cardiovascular disease, and that they speak only to mortality in the short span (2.5-7 years)– were all too often lost in translation. The important microvascular benefits of tight glycemic control were also too often ignored in the mainstream press in our view.

As a diabetes patient I am mystified by people who point to the ACCORD results and say that the increased mortality in the intensive glucose arm was due to the near-normal A1cs, rather than the overall treatment strategy used. Whatever the cause(s) of the trial result – weight gain, hypoglycemia, too rapid a reduction in A1c, glycemic variability, some drug effect or drug interaction, etc. – the idea

that a near-normal glucose level is in and of itself a negative thing goes against epidemiological data and just plain common sense. Taking a step back, people with such a view would seem to believe that for the purpose of cardiovascular disease risk, having diabetes is better than not having diabetes. And we know that the opposite is true. Bottom line, I think the increased mortality in the intensive arm of ACCORD points to the fact that we need a broader range of drugs and better strategies to lower blood sugar to near-normal levels. We need a strategy of lowering blood sugar that is not associated with whatever the cause of the ACCORD trial results were (weight gain, hypoglycemia, or whatever it was).

On new diabetes drugs, I'd like to briefly share my thoughts on this month's disappointing FDA advisory panel meeting. As you may already know, the FDA Endocrinologic and Metabolic Drugs Advisory Committee voted 14 to 2 in favor of requiring all new diabetes drugs to demonstrate cardiovascular safety in a hard outcomes clinical trial even in the absence of a cardiovascular signal. The argument in favor of such a requirement, which was presented most avidly to the panel by Dr. Steven Nissen, goes as follows: We already have diabetes drugs that lower blood sugar. Two thirds of people with type 2 diabetes die of cardiovascular disease. Therefore, we should require all new diabetes drugs to prove that they do not increase the risk of cardiovascular disease.

While clearly nobody wants diabetes drugs to be approved that increase cardiovascular disease risk, I think that a cardiovascular safety trial requirement for ALL drugs will chill the development of new diabetes drugs, and do very little for patient safety. The FDA already knows how to recognize what drugs might potentially increase cardiovascular risk; signals could be derived from animal data, clinical data, or mechanistic data. We don't disagree that the agency should be more cautious about drugs with a signal – perhaps GSK should have been required to do a cardiovascular safety study pre-approval for Avandia after it was noticed in clinical trials that the drug increased LDL cholesterol levels, for example. For sure agreements on post-approval trials should be better enforced, and we realize this is harder than it sounds. But why treat a drug that has absolutely no cardiovascular safety signals the same as a drug that does have a safety signal? This makes no sense to us. Notably, by slowing the development of new drugs, this plan will encourage the use of older drugs such as sulfonylureas that will not have to go through the trials. Irony abounds, since sulfonylureas are the only drug class that has been shown to increase cardiovascular risk (University Group Diabetes Program).

Jokingly (but not really), we characterize the FDA advisory panel meeting as the invasion of cardiologists into the land of diabetes. What the cardiology-dominated FDA advisory panel may not have fully appreciated in our view was the need for a broad range of diabetes drugs. Currently, almost eight million people with diabetes in the US are estimated to be over their glycemic target (<7%), and since many of the diabetes drugs that are used have significant side effects such as weight gain, hypoglycemia, gastrointestinal disturbances, etc. This may be why the panel dissenters – a pediatric endocrinologist (Dr. Eric Felner) and, notably, the only patient advocate on the panel (Rebecca Killion, who is interviewed in this issue of DCU) – voted the way they did. We wish that the ADA had made a statement representing the desires of the diabetes community as such a statement could potentially have swayed the committee. At this point, we can only hope that the FDA guidelines that are eventually implemented are reasonable – consider this our plea.

Sincerely,

Kelly L. Close

Major Headlines

In This Issue

Blogwatch

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

- **May 6:** Reporting bias — Insulin pumping in kids
- **June 17:** We're walking in DC…come join us!
- **July 9:** World Diabetes Day - B.L.U.E 2008
- **July 15:** CGM lovers, unite!

Videos

Below are our favorite YouTube videos in diabetes this month:

- "Triabetes – Being an Ironman is tough. Try doing it with diabetes" http://www.youtube.com/watch?v=XYI1fe7RMzQ&feature=related
- "Diabetes … RELOADED" http://www.youtube.com/watch?v=ZKHLmKGPUuM

Coming soon in DCU…

We're headed to three big meetings in the next three weeks in Washington DC, Florida, and back to Washington, DC – the Artificial Pancreas workshop this Monday and Tuesday, sponsored by FDA, NIH, and JDRF, the famed "Friends for Life" Children with Diabetes conference, which begins late next week, and the all-important AADE conference in early August, back in DC. Stay tuned…

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1. Quotable Quotes in Diabetes

"I thought the Banting Lecture was fantastic. It blended science with potential clinical implications in a way that seemed scientifically sound and understandable. Although I have not been a TZD user because I don't like weight gain, the arguments persuaded me to re-think early treatment with a triple therapy of metformin, exenatide, and a TZD, as a circumstance in which the metformin and exenatide might prevent TZD weight gain."

—Dr. Jay S. Skyler (University of Miami Miller School of Medicine, Miami, FL) commenting on this year's Banting Lecture by Dr. Ralph DeFronzo.

"When we begin to look at what diabetes puts people at risk for, cardiovascular risk is there, but please don't forget the microvascular risk."

—Dr. Robert Ratner (Georgetown University Medical School, Washington DC) reminding the panel on the FDA Advisory Committee Meeting (July 1) of the microvascular risks associated with diabetes.

"The road to hell is paved with biological plausibility."

—Dr. Steven Nissen (Cleveland Clinic, Cleveland, OH) referring to the problems that plagued the approval process for rosiglitazone and arguing for an across the board cardiovascular safety study requirement at the FDA Advisory Committee Meeting on July 1.

"I do not believe that the ADVANCE study should be taken, in any way, to negate the A1c guidelines produced by the ADA and other diabetes associations."

—Dr. Mark Cooper (Baker Heart Research Institute, Melbourne, Australia) presenting the ADVANCE study results at ADA.

"The people who really need closed loop are children."

—Dr. Bruce Buckingham (Stanford University, Palo Alto, CA) speaking about the feasibility of a closed loop system at ADA.

"If by this point in the meeting you're still unfamiliar with the word 'exenatide', you should probably ask the ADA meeting organizers for your money back."

—Dr. John Buse (University of North Carolina, Chapel Hill, NC) joking about the incretin focus of the ADA 68th Scientific Sessions during his presentation of 52-week data for exenatide once-weekly.

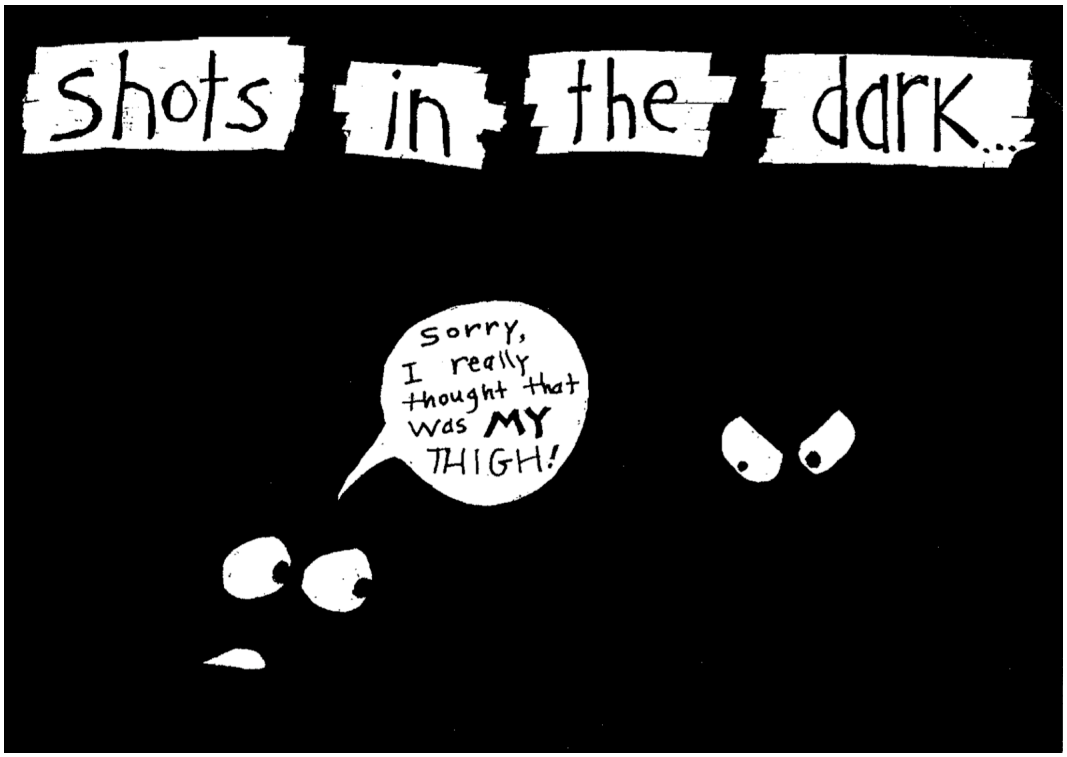
"Dr. Nissen said to the FDA advisory panel, 'I think that diabetes right now is glucocentric.' What I wanted to say was 'We're not treating heart disease. We are treating diabetes which is a glucose issue.' You better be focusing on the glucose because that is your problem. If you didn't have a problem with your glucose, you wouldn't have a chronic illness."

—Ms. Rebecca Killion (FDA patient representative) commenting on Dr. Nissen's statements to the FDA Advisory Committee Meeting that encouraged a cardiovascular outcomes study requirement for new diabetes drugs.

"There is no recognition that diabetes is different and that there may be people with diabetes who need a specific drug. As we discover more about different kinds of diabetes, we can say, 'There are some drugs that are indicated for one group of people and other drugs for another group.'"

—Dr. Harold Lebovitz (SUNY Brooklyn, New York City, NY) commenting on the why diabetes has not gotten the same amount of coverage as other diseases like cancer or cardiovascular disease.

2. diaTribe FingerSticks



— by Haidee Soule Merritt ©2007

3. DCU Company Watch

- **Novartis—Galvus development dropped for the US:** In Novartis's second quarter 2008 results press release on July 17, the company noted that it currently has no plans to resubmit Galvus (vildagliptin) to the FDA. During the call that followed, there was no mention of Galvus in the management's prepared remarks and no questions about Galvus during Q/A. We suspect that Novartis has dropped plans to resubmit Galvus because the FDA required a long and expensive clinical outcomes trial to address the concern of liver function impairment with the drug, and such a trial would have provided no guarantee of approval. By the time Galvus would have been approved, there likely would have been multiple other companies with marketed DPP-4 inhibitors such as Merck's Januvia (approved), Takeda's alogliptin (filed), BMS/AZ's saxagliptin (nearly filed, presumably), and Boehringer Ingelheim's BI1356 (phase 3). With a likely requirement for liver function testing if approved, Galvus would have been at a significant disadvantage against these other players in a crowded market.

  Galvus's misfortune stands in marked contrast to Merck's Januvia. The two DPP-4 inhibitors were neck-in-neck in development, and now Merck's Januvia is a blockbuster while Galvus is, though second to market, effectively nowhere close to Januvia. The two molecules are structurally very different – Januvia is a non-peptidomimetic, beta-amino acid-based molecule while Galvus is peptide-like and is hydrolyzed to inactive metabolite. These structural differences may have accounted for the dissimilar side effects that prevented Galvus approval in the US – Galvus was associated with liver function impairment in clinical trials, while Januvia was not. Some have speculated that Novartis also made Galvus side effects more visible to the regulatory agencies by

submitting a much larger, more comprehensive clinical package. Clearly, Merck will benefit substantially from Novartis' downfall in the US, as will whoever has the "next up" DPP-4 inhibitor in the US.

Galvus is being launched in Europe, where it was approved after months of setbacks on January 31, 2008. Also being launched in Europe is Eucreas, a fixed dose combination of Galvus and metformin. Galvus will be the second DPP-4 inhibitor marketed in Europe after Merck's Januvia. A major disadvantage for Galvus is that patients using the drug are required to have a liver screening conducted at the start of treatment, every three months after starting therapy for the first year, and then on occasion after the first year of therapy – this definitely increases the "hassle factor" involved with the drug and would be considered a major marketing negative. We understand that Galvus will be launched in India within the next month.

- **Biodel—Top-line interim VIAject phase 3 data looks promising:** On July 16, Biodel announced the completion of two of its phase 3 clinical trials for VIAject, the company's "very rapid-acting insulin." Unexpectedly, the company also released interim six-week data (n=563) and announced that results of the full trial will likely be released in a poster presentation at EASD. Top-line data indicated that after six weeks of treatment, there were significant differences between patients treated with VIAject or with regular human insulin (RHI) in weight gain, meal-time dose reductions, and mild to moderate hypoglycemic events in both type 1 and type 2 patients. In type 1 patients treated with VIAject (n=102), there was little to no weight change from baseline vs. 1.4 kg weight gain in the RHI group (n=108), a 34% reduction in prandial insulin dose compared to the RHI group, and approximately 16% fewer hypoglycemic events compared to the RHI group. For type 2 patients treated with VIAject (n=173), there was an average weight loss of 0.5 kg vs. 0.8 kg weight gain for the RHI group (n=180), a 36% reduction in prandial insulin dose compared to the RHI group, and 47% fewer hypoglycemic events compared to the RHI group.

  These results are impressive and appear to be superior to data from the phase 3 trials of the available rapid-acting insulin analogs, which were also compared to regular human insulin (the FDA considers regular human insulin to be "standard of care"). If VIAject is able to effectively be weight neutral or cause weight loss, reduce prandial insulin dose, and result in fewer hypoglycemic events, it could have significant advantages versus other diabetes drugs. We are very interested by the fact that treatment with VIAject shows less weight gain and a reduction in hypoglycemic events. These two effects may well go hand in hand – with fewer post-meal lows, diabetes patients may snack less frequently to "turn around" hypoglycemia, and weight gain would be reduced. We await trials against rapid-acting insulin analogs to confirm. As of July 16, only top-line data and two abstracts posted online for the 44th Annual Meeting of EASD have been released by Biodel; we eagerly await the publication of full six-month and one-year data.

- **Abbott—Single-digit diabetes care growth in 2Q08 benefit from strong int'l sales:** Abbott Diabetes Care (ADC) reported worldwide sales of $336 million reflecting 9% annual growth, which was bolstered strongly by currency – sans the currency benefit, we believe revenues were up a couple of percent year over year. ADC had terrific results internationally where sales rose 22% year over year on a reported basis and just over 8% excluding the impact of currency. These results were driven by strong currency as well as fast international adoption of the new no-coding meters Freestyle Lite and Freestyle Freedom Lite and especially good results in Latin American and Asian emerging markets. US revenues were weak, falling 5% year over year. Management attributed the decline to the 2Q07 launch of the FreeStyle Lite, which they said made for a tough comparison year on year. Actually, US revenue had risen just 1% in 2Q07, so we assume weakness likely stemmed from the combination of timing and increased competitive dynamics (J&J's US 2Q08 revenue increased 9%). However, in an unusual move management

gave guidance on the call for an anticipated global revenue increase of 10% during 3Q08. This was especially reassuring since ADC faces a difficult comparison of ~14% annual growth in 3Q07.

On the new product front, management mentioned the development of a combined meter, test strip, and lancet though no details on timing were given. Currently, three other integrated systems are on our radar, including Intuity Medical's OnQ (see our ADA report for more detail), Roche's Accu-Chek Compact, and Pelikan Technology's Pelikan Sun (see DCU #31). From our view, this reflects continued efforts by manufacturers to make systems both easier to teach as well as easier to use, definitely a positive in our view. We don't have any specifics on costs to create such systems, but that is always an important question. No revenue detail was given for FreeStyle Navigator, and no updates were provided on the Navigator/OmniPod integration between Abbott and Insulet. Despite this, we are increasingly positive on reimbursement prospects for CGM broadly speaking, which should have a positive impact on the entire industry in 2009 and beyond. The recently launched FreeStyle Freedom Lite was characterized as a growth driver.

Growth in Abbott's lipid control business continues to outpace the market, according to management – we know this area is increasingly important when thinking of patients with diabetes. Sales of Niaspan, a medicine that increases HDL, rose nearly 14% year on year, with quarterly sales of nearly $200 million. Phase 3 data on a new lipid control molecule called TriLipix was presented at this year's National Lipid Association Scientific Sessions and at ADA. TriLipix, an investigational molecule that may lower LDL and triglycerides while raising HDL, was submitted for FDA approval at the end of last year, and the company remains on track for the approval of this drug in 4Q08. We would look for heavy direct marketing to patients with diabetes since the data looks positive for lipid improvements in this sub-group.

- **J&J—Robust US sales lead impressive growth in 2Q08:** In a call led by J&J CFO Dominic Caruso on July 15, J&J reported robust global sales in its Diabetes Care franchise during 2Q08, with revenue of $674 million and a year over year growth rate of 13% (just under 7% without the impact of currency) making this one of the strongest currency impacts we can remember. The strongest areas for the Diabetes Franchise were in the US and at Animas, both of which appear to be steamrolling ahead. Domestic sales of $338 million increased an impressive 9%, just edging past the international division, which had sales of $336 million and a growth rate of nearly 18% year over year. Without the impact of currency, international growth for J&J's Diabetes Care franchise was 4% year over year, well below last quarter's 13% annual growth. This is the "closest" in revenue the US and international divisions have ever been to each other.

  Strong domestic revenue for the Diabetes Franchise was bolstered by the continued reported success of the OneTouch Ultra franchise. J&J will be introducing two new meters, including the OneTouch Vita, to be initially distributed in Europe only. Coding will not be required, and various features will help patients and healthcare providers assess impact of food choices and optimization of insulin therapy. Another key new meter will be the OneTouch UltraVue, to be distributed in Japan. As we understand it, the OneTouch UltraVue was developed in conjunction with Japanese key opinion leaders – it is said to be easy to learn and easy to use, and includes an on-screen tutorial and a hands-free strip ejector. To date, we believe LifeScan's blood glucose monitoring share of the market has hovered under 10% in Japan whereas a number of local companies "own" the market – lots of upside here in revenue and margin. The OneTouch Horizon meter shows that J&J remains committed to serving India and other developing markets. This device is a low-cost blood glucose meter that helps patients overcome the economic barriers to blood glucose testing and improved diabetes management. We have heard but are not sure yet whether the OneTouch Horizon will also be used in other emerging markets like Brazil, Russia,

and China. The OneTouch Flexx will provide wireless real-time data transfer of point-of-care glucose results – great to see movement in the hospital setting.

The launch of the integrated DexCom/Animas sensor augmented insulin pump (expected in 2009) could help maintain this growth and significantly augment it over time if conversion to continuous glucose monitoring continues. J&J's Animas franchise has seen growth averaging at least 30% for the last four quarters – again, very impressive given that Animas does not have a CGM option, does not have a disposable pump option, and competes in a market where the top player has 70%-plus market share. We believe international growth is bolstering Animas pump sales as well. Animas will face "tougher" comparisons in coming quarters but will also benefit from the brand-new OneTouch Ping as well as, in quarters ahead, with its own CGM/pump combination with DexCom.

J&J is also addressing the diverse needs of patient groups. The recent acquisition of Children with Diabetes, one of the most established online communities for young patients with diabetes and their families, will continue to provide new insights into the needs of families living with diabetes and promoting better care through its web site and conferences. We know providers in China will benefit from the J&J Diabetes Institute set to open in Beijing later this summer – in all, JJDI plans to train 10,000 providers globally in 2008, in Silicon Valley, California, Paris, Tokyo, and Beijing.

Lots of other goings-on at J&J of late – see our August DCU, DCU #82, for a download on J&J's recent analyst meeting and its inspired partnership with ResMed.

- **Novo Nordisk—Look for Liraglutide to be first-in-class GLP-1 in Japan:** On July 15, Novo Nordisk announced that it has filed liraglutide for regulatory approval in Japan, only 53 days after it filed for regulatory approval in the US and Europe. As a reminder, liraglutide is a once-daily human analogue of the naturally occurring hormone glucagon-like peptide-1 (GLP-1). Liraglutide was filed to obtain a monotherapy indication, as well as an indication for use in combination with a sulfonylurea. The Japanese phase 3 program included 678 patients with type 2 diabetes. This was the final part of the LEAD clinical trial program, which enrolled approximately 7,000 patients internationally.

  The phase 3 Japan data has not yet been published and is not expected at EASD. We are eager to see this data because it isn't yet known how well GLP-1s will "work" in Japanese patients broadly speaking. Asian type 2 patients are known to have "frail" beta cells that rapidly burn out, suggesting that liraglutide's potential beta-cell protective effects may be especially valuable in this population. On the other hand, liraglutide may not produce as robust weight loss in this population. In the 1,041 patient liraglutide study presented by Professor Michel Marre at ADA, liraglutide did not produce significantly more weight loss than placebo in the predominantly Asian study population.

- **Intel Corporation—FDA approves cool in-home care management monitoring system:** On July 10, Intel was granted clearance by the FDA to sell Health Guide for patients with chronic illnesses like diabetes and congestive heart failure. Health Care allows patients to monitor their health status by collecting data from external medical devices (e.g. glucose meters, blood pressure monitors, etc.). The information can then be securely stored and sent to clinicians who can remotely monitor their patients. Other interactive tools include multimedia educational content, video conferencing, vital sign collection, and patient reminders. The company has stated that pilot studies educating patients and clinicians about Health Guide have been completed in the US and UK, and the company expects Health Guide to be commercially available in the US and UK either late 4Q08 or early 1Q09. We welcome the sale of this product and hope it

encourages patients with diabetes to take a more active role in monitoring their health. We believe that it is a positive step towards facilitating interactions between patients and physicians leading to an improvement in healthcare management and possible reduction of future complications.

- **Orexigen—Second Phase 2b trial of Empatic underway:** Orexigen therapeutics announced on July 9 that it has initiated a second phase 2b study for Empatic, an anti-obesity drug candidate that combines the drugs zonisamide and bupropion . The phase 2b study, ZB-202, will enroll approximately 720 obese and otherwise healthy, non-diabetic patients at 20 sites nationwide. Subjects will be randomized for 24 weeks to one of two doses of Empatic, or to zonisamide or bupropion monotherapy arms, or to placebo. As a reminder, bupropion is a dopamine and norepinephrine reuptake inhibitor used to treat depression and smoking cessation, while zonisamide is an anti-epileptic drug. Interestingly, bupropion tends to be associated with agitation and an increased risk of seizures, while zonisamide has the opposite effect – this was likely the rationale for combining these two agents, both of which are associated with some weight loss in monotherapy. We note, however, that zonisamide is included on the list of anti-epileptic drugs for which the FDA issued a warning in February 2008 because of a doubling of the risk of suicide in patients taking the drugs.

  In order to progress to phase 3, Orexigen will need to demonstrate to the FDA that Empatic is superior to its monotherapy components. The primary endpoint of the study is percent change in body weight after 24 weeks of blinded therapy. In one arm of the first Empatic phase 2b trial, subjects achieved a weight loss of 11-15% with a discontinuation rate of ~17%. Empatic lags about 18-24 months behind the development of Contrave, Orexigen's phase 3 obesity candidate.

  Based on the available clinical data, Empatic appears to be somewhat more effective than Contrave, which produced 8.0% to 10.7% weight loss among patients completing phase 2 studies. Empatic may also have a milder adverse event profile (Contrave was associated with dose-dependent nausea with 18% discontinuation in phase 2 studies due to nausea in the high-dose group, as well as some non-postural dizziness, though no serious adverse events were reported). It's difficult to compare the two drugs, of course, without a head-to-head. Orexigen has indicated that if both Contrave and Empatic are eventually approved, Contrave will be marketed primarily to female patients with mild-to-moderate obesity, emphasizing that Contrave may target the behavioral aspects of eating (craving, food obsession, etc.). As a reminder, Contrave combines bupropion (which is marketed for smoking cessation) with naltrexone, a drug used to treat opioid dependency. As we understand it, Empatic will instead be positioned as a treatment for moderate-to-severe obesity, as an alternative to bariatric surgery.

- **Animas—FDA approves Ping, enabling wireless communication between new blood glucose meter and pump:** In the latest move to integrate insulin pump and glucose-meter technology, Animas announced on June 30 that the FDA has approved its OneTouch Ping Glucose Management System which is wirelessly linked to the OneTouch Ping pump. The main advantage of this system is that after testing blood sugar with the meter, the patient can send insulin dose information wirelessly to the pump without ever having to touch the pump. Blood glucose and pump data can be downloaded either from the pump or the meter to a Mac or a PC. Like the 2020, the pump is waterproof and has the popular color screen. This integrated approach is what many intensively managed patients seek, and this customer base is important for LifeScan and Animas in our view as type 1 management continues to move toward more intensive control. The Ping begins shipping in August (in time for AADE) and patients can order a Ping system either as an upgrade at a reasonable (still undisclosed) cost or as a brand new system.

We believe this new pump will reap benefits from other recent structural changes at J&J. For example, the J&J Diabetes Institutes (open in Japan and Silicon Valley and set to open in Beijing and France shortly) will see thousands of healthcare professionals who will have the chance to learn more about pumping, and will presumably practice with this system. This approval and launch should be a win for Animas, as will the launch of the combined 2020 and continuous monitoring system, which is expected next year. We have been very impressed that Animas has continued to gain market share while competing with Medtronic's Paradigm (the only integrated pump/CGM currently available) and Insulet's disposable OmniPod. We believe Animas should be able to continue to expand its market share with the Ping while also setting the stage for the next integrative effort in device technology.

- **EnteroMedics—One-year VBLOC-RF2 feasibility study results released:** On June 27, EnteroMedics released top-line one-year weight loss results for the 12 patients enrolled in the extension of the VBLOC-RF2 feasibility study. VBLOC therapy, administered by the company's Maestro System, uses high-frequency, low energy electrical impulses to intermittently block vagus nerve signals, thereby reducing appetite. EnteroMedics management has previously described VBLOC therapy as fitting somewhere between current pharmacotherapy and surgery options for obesity because it is less invasive than bariatric surgery (VBLOC therapy is reversible with no food restrictions and no need for future adjustments). At the end of one year, patients had an average excess weight loss (EWL) of 29.1%. This compares positively to EWL of 27.4% at nine months of therapy (17 patients) and 21.4% at six months of therapy (28 patients). The continued weight loss trend is encouraging, but it appears to slow down significantly after nine months of therapy, and we believe that weight loss will likely plateau around 30%. Given the small number of patients enrolled in the extension study, it is difficult to assess whether the continued weight loss trend is significant and it's hard to know, from the design, how hand-picked the patients were and the extent to which diet and exercise influenced the results.

  During a conference call that followed the release of these study data, management provided an update on enrollment of the EMPOWER study. This one-year study is being conducted at 15 sites in the US and Australia. EnteroMedics hopes to use data from the EMPOWER study to support a PMA for the Maestro System in mid-2009, targeting commercialization in early 2010. Management said that the drop-out rate in the EMPOWER study has been lower than previously expected, and therefore the company expects to complete enrollment by the end of June with approximately 300 total subjects. This estimate is at the upper end of the original enrollment estimate of 220 to 300 subjects.

- **Melior/Pfizer—Transformation of anti-ulcer drug to diabetes compound:** On June 25, Melior Discovery Inc. announced a collaboration with Pfizer to develop a compound for diabetes named MLR-1023 (tolimidone). Pfizer, which patented tolimidone in 1975, originally developed the drug as a potential anti-ulcer medication. The drug was studied through phase 3 in 1980 but never marketed due to lack of efficacy. However, Melior has recently found through *in vivo* screening that the compound also has anti-diabetic properties.

  To our knowledge MLR-1023 is a first-in-class diabetes drug. It may work by activating LYN kinase, a tyrosine kinase that phosphorylates and activates insulin receptor substrate-1 (IRS-1). This protein, which is normally activated by the insulin receptor, in turn activates a signaling pathway resulting in the stimulation of glycogen synthesis as well as increased affinity of facilitated glucose transporters like GLUT-4. In addition, MLR-1023 is weight neutral or causes weight loss in preclinical models, although Melior does not plan to develop the drug for obesity. According to Melior, the combination of MLR-1023 plus a TZD may be weight neutral. MLR-1023 is not likely to cause hypoglycemia, and in preclinical models it is as effective as metformin.

Melior has indicated that it is "nearly ready" for phase 1 clinical trials. Although the compound has previously been investigated through phase 3, testing of MLR-1023 for diabetes will begin in phase 1 because GLP/GXP standards have changed since the original clinical trials for this compound. Nonetheless, we believe that it is likely that clinical development will proceed more rapidly than other comparable compounds because of the significant clinical data already available for tolimidone.

The financial terms of Melior's agreement with Pfizer have not been disclosed. According to Melior, the company has granted Pfizer an option to negotiate a license to MLR-1023 following a phase 2a clinical trial. Broadly speaking, we believe that the agreement highlights Pfizer's increased interest in the field of diabetes. Since the discontinuation of Exubera in late 2007, Pfizer has described diabetes in its analyst day and at other venues as a "disease area priority."

- **Osiris Therapeutics—Two million dollar milestone payment from JDRF:** On June 25, Osiris Therapeutics announced that it had received $2 million in milestone payments from the Juvenile Diabetes Research Foundation (JDRF) for progress made on Prochymal, a mesenchymal stem cell therapy for people recently diagnosed with type 1 diabetes. Certain clinical and regulatory milestones had been achieved in its phase 2 clinical trial, prompting the payment. Prochymal is now in phase 3 trials, and the FDA has given it fast-track status.

  Prochymal treatment aims to delay and possibly halt the progression of type 1 diabetes in the hopes of preserving islet cell function and preventing complete destruction of the beta cells. Prochymal homes in to sites of inflammation and has shown promising results in treating other immune-mediated diseases including graft vs. host disease and Crohn's disease. Its ability to inhibit the immune system is a critical step in finding a treatment for type 1 diabetes because it may prevent beta cell loss, saving pancreatic insulin production. Mesenchymal stem cells have been shown to have a significant inhibitory effect on the immune system, and we look forward to seeing the results of the phase 3 trial for Prochymal.

- **Emisphere/Novo Nordisk—Partnership to develop oral GLP-1:** On June 23, Emisphere and Novo Nordisk announced a partnership agreement to develop an oral formulation of a GLP-1 analog. By the terms of the agreement, Emisphere may receive from Novo Nordisk at least $87 million in product development and sales milestone payments as well as undisclosed royalties on sales. The minimum first year payment is $10 million. Novo Nordisk will be responsible for the development and marketing of drug candidates.

  In our view, it is too early to speculate on the viability of an oral GLP-1 product candidate, but we are not surprised to see alternate deliveries being explored. On the positive side, oral GLP-1 is likely to be safe because native GLP-1 is produced along the digestive tract, the location where an oral GLP-1 would be absorbed. Also, GLP-1 analogs have been shown to have a wide therapeutic index; thus, precise dosing is unimportant (little or no hypoglycemia in monotherapy). If successful, we believe that such a product might compete not only with subcutaneous GLP-1 but also with DPP-4 inhibitors because it could be positioned as delivering superior efficacy and clinically meaningful weight loss. On the negative side, a potential problem with oral GLP-1 is that bioavailability may be low. Low bioavailability would mean larger pills and higher costs. Alternate routes of administration of peptide hormones such as insulin and GLP-1 have often looked better in writing than in practice, and in the case of oral GLP-1, we await more information.

  The partnership follows Novo Nordisk's decision in April of this year to terminate all pulmonary delivery activities including inhaled GLP-1. It is unclear to us if Novo Nordisk is very serious about developing an oral GLP-1, or whether it simply wants to have a hand in the game just in

case it works. The company had this strategy with inhaled insulin – the company invested in a candidate in case it worked, but it invested far less money than Pfizer.

- **Novo Nordisk—Top-line Liraglutide data emerges for obesity:** Novo Nordisk released top-line open label obesity data for an extension study (from 20 to 52 weeks) of the phase 2 trial of liraglutide for obesity on June 12. Liraglutide is Novo Nordisk's lead GLP-1 analog, which has been filed in the US for diabetes and is moving to phase 3 for obesity. By the end of 52 weeks, patients using the highest dose of liraglutide achieved a mean weight loss of 7.5 to 8.0 kg (5.5 to 6.0 kg placebo-adjusted) from a baseline of ~100 kg (average placebo-controlled weight loss of ~6%). Approximately 75% of the trial participants receiving the highest dose of liraglutide had a weight loss from baseline larger than 5%, and more than 35% of the participants achieved a weight loss greater than 10%. This result compared favorably to weight loss in the placebo group, in which approximately 25% of participants achieved weight loss greater than 5%, and 10% of participants achieved weight loss greater than 10%. The results are also much better than for the comparator drug, orlistat (Roche's Xenical); approximately 45% of the participants receiving orlistat achieved a weight loss greater than 5%, and 15% achieved weight loss greater than 5%.

  This amount of weight loss was larger than in many prior diabetes trials of liraglutide, presumably because higher doses of the drug were used. This observation is consistent with several studies that have shown that the anti-diabetic effects of GLP-1 therapy "max out" at lower doses than the weight-loss effects. We aren't sure what doses of liraglutide were used in the trial beyond knowing that participants received the "diabetes dose" and above (presumably 1.8 mg and above). Approximately 15% of participants in the liraglutide arm of the study withdrew due to side effects. This was a lower dropout rate than we would have expected – obesity trials historically have dropout rates of 50% and higher.

  The most impressive result of the trial in our view was the rate of remission of prediabetes in the liraglutide arm. At the time of first randomization, 30% of participants in the extension study showed evidence of prediabetes. At the conclusion of the extension study, 80% of the prediabetes subgroup within the high-dose liraglutide treatment group ceased showing signs of prediabetes, compared to approximately 30% for the placebo and orlistat treatment groups.

  Although the level of weight loss achieved in the study does not significantly raise the bar above current oral therapies, we believe that physicians may favor liraglutide because of its improved side effect profile and presumed safety profile. Whereas sibutramine and many oral therapies in late-stage development act on the central nervous system, we believe that there is great medical interest in treating obesity by leveraging peripheral hormones, which may be intrinsically safer. The development of liraglutide for obesity and prediabetes also jives with an increased interest amongst diabetologists in treating diabetes earlier in its progression. Given liraglutide's presumed safety, the potential for beta-cell preservation (though it is not proven in humans), and weight loss, we could ultimately see liraglutide becoming a widely used prediabetes drug if it moves through regulatory hurdles.

- **Vivus—Qnexa potentially promising for diabetes:** The results of Vivus's OB-202 study of Qnexa in type 2 diabetes were presented by Dr. Timothy Garvey (University of Alabama at Birmingham) on June 10 at ADA. Qnexa (VI-0521), which combines phentermine (an approved short-term appetite suppressant for weight loss) and topiramate (an approved anticonvulsant), is in phase 3 for obesity and is also under investigation as a diabetes drug. Based on the data presented, we believe that it is likely that Qnexa, if approved for obesity, will receive a secondary indication for diabetes.

The 28-week OB-202 study randomized approximately 200 patients to receive Qnexa (15 mg phentermine and 100 mg topiramate) or placebo. Qnexa was found to decrease A1c levels by 1.2% compared to 0.6% in the placebo arm. The mean baseline A1c was 8.6%. Forty percent of Qnexa patients achieved a 7% A1c target compared to 25% in the placebo group; 25% of Qnexa patients and 7% of placebo patients achieved a target of 6.5%. Qnexa also reduced cardiovascular risk factors such as blood pressure and lipid levels, and resulted in an 8% reduction of body weight vs. 1.2% in the placebo arm. Qnexa treatment caused an increased incidence of side effects, but they did not result in higher withdrawal from the study. Treatment increased the incidence of nausea by 13%, constipation by 6%, and caused paresthesia in 17% of subjects. However, the withdrawal rate in the treatment arm was actually lower than in the placebo arm (3% compared to 4%).

Whether or not Qnexa is shown to be safe and effective in phase 3, we think that this study is significant in that it validates weight loss as an effective means of controlling blood glucose. We look forward to the clinical results of other obesity drugs in diabetes.

- **Roche/Ipsen—Once-weekly GLP-1 (taspoglutide) moves to phase 3:** Taspoglutide (R1583), a once-weekly GLP-1 analog in development by Roche and Ipsen, was a major focus of the Roche's investor meeting on July 9 at ADA. During the investor conference it was announced that taspoglutide is now in phase 3 and that phase 3 trials will include superiority trials against Byetta, Januvia, and Lantus. The company hopes to file taspoglitide in mid-2010. During the investor meeting, taspoglutide was described as having distinct advantages against "a twice-daily competitor" (presumably Byetta), "a competitor once-weekly" (presumably exenatide once-weekly) and "a competitor once-daily" (presumably liraglutide). Without phase 3 data, we think it is on the early side to make claims about advantages and disadvantages, but the stated advantages at the investor conference were:
    - Vs. Byetta – better efficacy (to be proven), human GLP-1 based vs "reptilian", 1/14th the number of injections.
    - Vs. Liraglutide – better efficacy (to be proven), a starting dose that is therapeutically effective, 1/7th the number of injections, and two steps instead of three.
    - Vs. (exenatide once-weekly) – 29 gauge vs. 23-27 gauge, human GLP-1 based vs "reptilian", no reconstitution, easier to use injection device, effective starting dose, no run in phase with different device or schedule.

  Taspoglutide is two amino acids different from human GLP-1 (therefore, like liraglutide, it is not exendin-4 based). It is DPP-4 resistant and it includes zinc for a protracted absorption profile. Although it was studied as a once-every-two-weeks drug in phase 2, this was much less effective than once-weekly dosing and we presume that it will be developed as a once-weekly drug.

  Taspoglutide phase 2 results were presented at ADA and were generally very positive. In an eight-week study of taspoglutide as an add-on to metformin presented by Dr. Michael Nauck, MD (Diabetes Centre, Bad Lauterberg, Germany), the 20 mg once-weekly (QW) dose provided the best effect, with placebo-subtracted A1c drop of 1.0% from baseline 7.9% and weight loss of 2.0 kg. Notably, the downward trends in A1c and weight looked like they would continue past eight weeks with longer treatment, which leaves open the question of what the 'real' efficacy of Roche's compound is. A separate dose-ranging study presented by Dr. Robert Ratner, MD (MedStar Research Institute, Washington DC) at ADA showed that 20 mg once weekly is the optimal dose for taspoglutide. Higher doses produced more GI adverse effects with no additional efficacy. Nausea and vomiting were most prevalent after the first and second weekly injections and were usually transient. From the numbers he showed, it looked like nausea, diarrhea, vomiting, and dyspepsia rates were roughly 2-3x compared to placebo in the 20 mg group, and 2x higher still in

the 30 mg and 40 mg groups. The study was not powered to look at efficacy but A1c did fall from ~7.9% to ~6.7% for taspoglutide vs. ~7.5% for placebo. Dr. Ratner emphasized that FPG fell very quickly (within the first week), showing that this drug has a fast onset of action – we assume this was a tacit comparison to exenatide once weekly. No pruritis (itching), nodularity, or infections were observed at the injection sites. Low titer antibodies were found in only three patients – we note that this is quite low for a GLP-1 agent. There was no severe hypoglycemia in the study.

- **Amylin/Lilly—Exenatide once-weekly achieves 2.0% A1c drop at 52 weeks:** ADA President Dr. John Buse presented 52-week exenatide once weekly (QW) data from the DURATION-1 study during a late-breaking oral session on June 9 at ADA. As a reminder, the DURATION-1 study was designed to show non-inferiority of exenatide QW to Byetta twice daily (BID). The study randomized 295 type 2 diabetes patients with a mean A1c of 8.6 to 30 weeks of treatment with 2.0 mg exenatide QW or 10 mcg exenatide BID. As previously reported, exenatide QW showed superiority over Byetta at the end of 30 weeks; the A1c drop was 1.9% for QW and 1.5% for BID. Weight loss was 3.7 kg with QW and 3.6 kg with BID. At 30 weeks, all patients were invited to enter a 22-week open-label extension study with exenatide QW. All patients were either continued on or switched to exenatide QW. This study included 241 of the 295 original patients. Withdrawals prior to week 30 were 13.5% and 11.6% for QW and BID, respectively. Withdrawals after week 30 were 4.1% and 6.1% for QW and BID, respectively.

  In the 22-week extension, exenatide QW was associated with durable glycemic improvement. On average, patients achieved a 2% reduction in A1c at 52 weeks; 72% achieved A1c <7% and 54% achieved A1c <6.5%. Mean final A1c was 6.6%, and mean weight loss was 4.3 kg. Further improvements in glucose control were observed in subjects who switched from exenatide BID to exenatide QW, with similar final results among those who remained on QW and those who switched. Both groups had clinically significant reductions in systolic and diastolic BP. There was no major hypoglycemia, and for patients not on a sulfonylurea, no minor hypoglycemia. The safety profile for QW was consistent with BID with some additional local injection site irritation, which resolved after the first six months of therapy. The transition from BID to QW was not associated with new or additional adverse effects.

  Overall, the sustained efficacy of exenatide QW at 52 weeks was not unexpected, but it is nonetheless very positive. The 2.0% A1c drop in the study will certainly turn heads among patients and healthcare providers. The only concerning signal in the trial was the increased rate of local injection site irritation in the exenatide QW arm relative to the BID arm. This is likely due to the increased needle size for exenatide QW; the needle used in the trial was a 23 gauge, although Amylin purports to be optimizing the injection device and may reduce the size of the needle to a 25 gauge or even 27 gauge in the final product presentation.

  Amylin also released a series of posters at ADA describing patient views of their diabetes treatment experience comparing exenatide QW and Byetta in DURATION-1. Patients using exenatide QW seemed to be equally or more satisfied with treatment than patients using BID, and reported similar positive and negative effects of treatment. Notably, of the subset of DURATION-1 subjects who were surveyed, approximately 68% (N=19) of the exenatide BID group and 90% (N=27) of the exenatide QW group said the most satisfying aspect of their treatment was that it worked well – this bodes well for potentially increased patient satisfaction in our view when exenatide once weekly hits the market. One area in which the treatments differed was injection problems, with more QW patients reporting difficulty (23% for QW vs. 11% for BID). This is actually lower than we had assumed given that the needle gauge for the first generation is not yet as optimized as we assume it will eventually be.

- **Amylin—Symlin shows strong data for mealtime insulin**: Dr. Matthew Riddle (Oregon Health Sciences University) presented impressive data during a late-breaking oral session on June 9 at ADA showing that adding a fixed mealtime dose of pramlintide (Symlin) to titrated basal insulin causes improvements in glycemic control equivalent to mealtime insulin. The 24-week study enrolled 112 type 2 patients with a mean A1c at baseline of about 8.3%. Patients in the Symlin arm were initiated immediately on basal insulin (Lantus or Levemir) and 120 mcg pramlintide prior to major meals, with down-titration to 60 mcg if necessary to limit nausea. Patients in the mealtime insulin arm were initiated on Humalog, Novolog, or Apidra after four weeks to allow adjustment of basal insulin first.

  By the end of the 24 weeks, A1c reductions were similar for the Symlin and mealtime insulin groups. Symlin caused more nausea (22% vs. 0%) but less hypoglycemia (82% vs. 55%) than mealtime insulin, and no change in weight (-0.3 kg) vs. weight gain (+4.2 kg) for mealtime insulin. Approximately 30% of Symlin and 11% of mealtime insulin subjects achieved the composite primary endpoint of 1) A1c <7%, 2) no increase in body weight, and 3) no severe hypoglycemia.

  Overall, the results indicate that Symlin is a viable replacement for mealtime insulin in some type 2 diabetes patients, and may have distinct advantages, notably less weight gain and hypoglycemia. The FDA has previously rejected a type 2 diabetes indication for Symlin as mealtime adjunct to basal insulin – we don't understand why since there are no safety issues and we consider this a disservice to patients, most of whom don't know the drug was being considered as an alternative. We have not been able to gain a good understanding of the FDA's basis for the rejection. The inclusion of this study in the late breaker session suggests it was warranted on a scientific basis and we look to FDA to turn around its position on this front in fairness to patients, providers, and the public (taxpayers, after all, are also impacted by patients who can't or won't adhere to mealtime insulin therapy).

- **BMS/AZ—Dapagliflozin (SGLT2 inhibitor) results impress at ADA:** Bristol-Myers Squibb and AstraZeneca presented long-awaited 12-week data for dapagliflozin, the companies' SGLT2 inhibitor in development for both type 1 and type 2 diabetes, in an oral session on June 9 at ADA. Dapagliflozin is the most advanced SGLT2 inhibitor in development, and the phase 2 data was therefore an important opportunity to assess the viability of this new drug class as a whole. The drug class works by reducing re-absorption of glucose from the urine back into the bloodstream, thereby promoting glucosuria (loss of glucose in urine). The kidneys usually reabsorb about 180 g/day of glucose from the urinary filtrate, and 90% of it is reabsorbed by sodium glucose cotransporter-2 (SGLT2).

  Dapagliflozin efficacy was quite impressive overall in our view. The middle dose of drug was associated with a mean 0.85% reduction in A1c from a mean baseline (and fairly low one) of 8.0% A1c. This compared to a 0.18% reduction in A1c for the placebo arm and a 0.73% reduction in A1c for the metformin arm. The same dose of dapagliflozin was also associated with almost 3% weight loss. Weight loss is expected with this drug class because of the loss of 100 to 300 calories of glucose per day in urine, and some companies including GSK are developing SGLT2 inhibitors for an obesity indication. While 3% may seem like "nothing to write home about," we think this is marketable because weight gain is the expectation for anyone going on TZDs and insulin and only one class, GLP-1, is on record as prompting weight loss.

  Safety and tolerability results appeared positive as well, and many of the theorized side effects of SGLT2 inhibition such as polyuria, urinary tract infections, and altered serum electrolyte concentrations did not surface in high numbers in the 400-patient trial. With dapagliflozin

moving to phase 3 and at least six other SGLT2 inhibitors in clinical testing – including GSK/Kissei in phase 2, Sanofi-Aventis in phase 2, Astellas/Kotobuki in phase 2, Mitsubishi Tanabe Pharma/J&J in phase 1, and Roche in phase 1 – we believe that the data bode well for SGLT2 inhibitors as a class. Of course, particularly in this political climate, we await more robust data to confirm safety and tolerability and it will be important to see safety data reproduced in larger patient numbers.

- **Takeda—Alogliptin phase 3 data look like Januvia:** Takeda presented its large alogliptin phase 3 dataset (N=2,514) in six separate posters on June 7 at ADA, including results from alogliptin monotherapy as well as add-on to sulfonylurea, metformin, TZD (pioglitazone), and insulin. Alogliptin is Takeda's DPP-4 inhibitor, which was filed in the US in early January 2008 and remains in phase 3 in Europe and phase 2 in Japan. Unsurprisingly, the efficacy, safety, and tolerability data look very similar to Merck's phase 3 Januvia data. The two DPP-4 inhibitors are very similar in structure; both are non-peptidomimetics that are not metabolized and are excreted renally.

  In monotherapy, the 12.5 mg once-daily dose of alogliptin was associated with an average A1c drop of 0.54% at 12 weeks from a baseline of approximately 8.0%. The minimum A1c was achieved in 8-12 weeks. In all of the phase 3 studies, efficacy increased only slightly from 12.5 mg to 25 mg, and doses above 25 mg provided no additional efficacy. Notably, the efficacy of alogliptin appears to be enhanced when it is used with Actos background therapy. In one study, alogliptin reduced A1c by 0.7% from a baseline of ~8.4% A1c when used as an add-on to pioglitazone (relative to pioglitazone alone). We believe that this result is important because Takeda intends to produce a combination alogliptin/Actos drug.

  Similar to Januvia, the adverse events reported in the alogliptin phase 3 data include nasopharyngitis (i.e. common cold), headache, and upper respiratory tract infection. There was no mention of liver toxicities (which have postponed the approval of Novartis's vildagliptin), or of Stevens-Johnson Syndrome or other exfoliative skin disorders, which have been reported in a small number of patients taking Januvia. Interestingly, a small amount of weight loss was observed relative to placebo although we question whether the weight loss described in the dataset is of clinical significance. While we believe that the weight-neutral characteristic of DPP-4 inhibitors has been important for their success relative to other classes such as TZDs and sulfonylureas, we believe that GLP-1 analogs will continue to distinguish themselves with weight loss. Based on the large number of patients who were dosed in Takeda's phase 3 program, we think that it is likely that alogliptin will be approved for multiple uses (e.g. monotherapy, add-on to other common agents), although we appreciate that the hurdle for FDA approval has likely grown since the time that Januvia was filed.

  The alogliptin data suggest that if it is approved as expected, it and Januvia will likely be perceived as near-equivalents in the eyes of healthcare providers. Januvia will continue to benefit from a first mover advantage and more long-term safety data. Nonetheless, we believe that with Januvia sales for 2008 expected at well over $1 billion and with the DPP-4 inhibitor class likely to continue to achieve robust growth as physicians move away from TZDs and sulfonylureas, there is certainly room for another player. Pharmaceutical Product Development, Inc., which assisted Takeda in the development of alogliptin, stands to receive additional development milestones if the filings and approvals are made and obtained in other regions of the world, as well as sales-based milestones. OSI, which has method-of-action patents in the DPP-4 space, also stands to benefit if Takeda expands the DPP-4 inhibitor market.

- **BMS/AZ—Partial phase 3 data for saxagliptin published at ADA – and a name emerges, Onglyza:** Bristol Myers-Squibb (BMS) and AstraZeneca (AZ) released some phase 3 data for their DPP-4 inhibitor, saxagliptin, in a poster presentation on June 7 at ADA. Unsurprisingly, the data looked very similar to Merck's Januvia and Takeda's alogliptin – we don't think any late-stage drugs in this class will differentiate themselves on the grounds of efficacy or probably even selectivity. Starting from a baseline A1c between 7.0% and 10.0% (mean A1c of 7.9%), the 2.5, 5, and 10 mg doses of saxagliptin as a monotherapy were associated with placebo-subtracted A1c reductions of 0.62%, 0.64%, and 0.73%, respectively, at 24 weeks. Similar to other drugs in the class, saxagliptin was weight neutral in the study.

  Encouragingly, the abstract reports that the frequency of adverse events was similar across all treatment groups (saxagliptin and placebo). There was no mention of Stevens-Johnson Syndrome or liver toxicities, and BMS investigator Dr. Roland Chen confirmed for us in a conversation at ADA that no such side effects have been observed within the entire phase 3 saxagliptin program. The one concerning side effect, in our view, was a "small decrease in mean lymphocyte count" associated with the highest saxagliptin dose, although the poster notes that there was "no evidence of clinical sequelae." Given saxagliptin's structural similarity to Novartis's Galvus, which has been held up by the FDA on safety concerns, we continue to watch saxagliptin's clinical data closely and we look forward to the full phase 3 dataset. Saxagliptin apparently remains on track for a mid-2008 filing, and BMS/AZ have announced that the drug will be marketed under the trade name Onglyza.

- **Generex—Dosing patients in Oral-lyn phase 3 trial:** On June 5 Generex announced that it has commenced dosing of patients in a six-month phase 3 trial of Oral-lyn, the company's oral insulin spray. The phase 3 study is enrolling approximately 750 patients with type 1 diabetes in 36 centers in the US, Canada, Russia, and Eastern Europe. In the study, Oral-lyn will be compared to prandial injections of regular human insulin; the primary endpoint is change in A1c. Oral-lyn is a formulation of regular insulin that is absorbed buccally, not in the lungs. Based on previous trials of Oral-lyn showing similar kinetics to prandial regular insulin, we expect that efficacy will be similar to regular human insulin. In order to receive FDA approval, the company will look to demonstrate non-inferiority to regular insulin in phase 3. Oral-lyn has been approved in Ecuador and India. While there are clear questions about cost and some about safety, we are interested to see large-trial results.

  Even so, if Oral-lyn is shown to be safe and effective in phase 3, several potential downsides remain. With a bioavailability of approximately 10%, the typical type 2 patient may need to take 30 puffs of Oral-lyn daily, which could spell hassle for many – although for others it may well be a welcome alternative. More concerning, the low bioavailability also suggests that large volumes of insulin will need to be used, increasing cost of the therapy. An additional problem for young children or patients that are particularly insulin-sensitive is that Oral-lyn can only be administered in full units, not half units. Nonetheless, Oral-lyn will likely be cheaper than insulin analogs and may be an attractive option for some children and patients with an aversion to needles. While that percentage of total patients may be low overall, the burgeoning volume of total patients (there are now 18 million diagnosed in the US alone) and the average A1cs suggest that a number of drug alternatives may be welcome – along, we would say, with important education alongside the therapy.

- **Novo Nordisk—Liraglutide leads Byetta in top-line LEAD-6 results, and questions emerge:** Coinciding with the ADA, Novo Nordisk announced positive top-line LEAD 6 results comparing liraglutide, the company's once-daily GLP-1 analog, against Byetta (Amylin/Lilly). The top-line results showed a 1.1% A1c reduction for the liraglutide group vs. a 0.8% A1c reduction for

the Byetta group from a baseline of slightly over 8%; this was a statistically significant difference. The percentage of patients achieving the ADA target of <7% was approximately 55% for liraglutide compared to 45% for Byetta. Nausea was roughly the same in both groups, around 25%. Weight loss was also roughly the same in both groups, with an average weight loss in both arms of approximately 3 kg. As expected, rates of hypoglycemia were low in both arms and were slightly lower in the liraglutide arm.

Although the statistically significant superior A1c reduction for liraglutide is clearly a win for Novo Nordisk, it is difficult to read deeper into the results without access to the full dataset and detailed methodology. For example, details about the patient population and dosing information have not been disclosed. The results for the Byetta arm of the study seem somewhat inferior to many other trials of the drug; previous studies of Byetta have typically produced an A1c reduction of 0.9% to 1.5%. This leads us to wonder, as a number of analysts have, if many patients were kept on the 5 mg dose rather than the higher 10 mg dose. However, regardless of the methods used, we think that liraglutide's top line results combined with the advantage of a once-daily medication will present a very marketable drug for Novo Nordisk's vast diabetes sales force and will do much to expand the GLP-1 market. We strongly believe Novo Nordisk will do an excellent job on further educating the healthcare community on GLP-1 and on expanding the market, both in the US and internationally – notably, it will have the first GLP-1 in Japan.

While it's hard to compare trials that aren't head to head, LEAD-6 suggests that liraglutide will likely be inferior to exenatide once-weekly with regard to efficacy. Looking at the data from LEAD-6, one could argue that liraglutide is similar in efficacy to exenatide once-weekly because the differences in A1c between Byetta and liraglutide in LEAD 6, and Byetta and exenatide once-weekly in DURATION-1 are similar (0.3% [difference between 1.1 and 0.8 drop] and 0.4% [difference between 1.5 and 1.9 drop], respectively). However, there are various questions about the methods of the study, and to date no single trial of liraglutide has posted an A1c drop equal to the 2.0% A1c reduction shown by exenatide once weekly in the DURATION-1 study. Regardless of which compound is most effective in lowering A1c, we believe that the commercial success of liraglutide and exenatide once-weekly is likely to depend more on nausea and the simplicity and comfort of administration and titration than efficacy ("hassle factor," for short, for both patient and healthcare provider).

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

4. Conference Pearls: ADA Annual 68th Scientific Sessions

June 6-10, 2008 • San Francisco, CA • scientificsessions.diabetes.org

More than 13,000 people attended the 68th Scientific Sessions of the American Diabetes Association, held in San Francisco's Moscone Center from June 6-10. The HUGE conference contained a remarkable eight tracks, 200 exhibits, and 2,840 oral and poster sessions. Below we share what we view as the most important themes from the conference. We have also reviewed some of the most important company data presented at the meeting in Company Watch (above).

- **All three of the large clinical trials that reported at the meeting, ACCORD, ADVANCE, and the VADT, failed to show a significant benefit of intensive glucose control on cardiovascular outcomes.** While there are many possible explanations for why intensive glucose control did not reduce macrovascular complications in the three trials (too short a timeframe, too old/sick a population, too quick an A1c reduction, glycemic variability, too much

hypoglycemia, too much weight gain, etc.), we think that the overall conclusion is negative for intensive glucose control. On the positive side, ADVANCE did show a significant reduction in microvascular complications (the microvascular data from ACCORD and the VADT will be presented in the fall at EASD). Nonetheless, we believe that the macrovascular results from the studies may shift some focus from tight glycemic control to tight lipid and blood pressure control, which did provide tangible macrovascular benefits over the lengths of the studies. We also look to long-term follow-ups of patients enrolled in the studies to see what longer-term effects intensive glucose control has on cardiovascular outcomes (see page 28 for more details).

- **ADA 2008 was more of a drug meeting than a device meeting – and, as such, more of a meeting about type 2 rather than type 1 diabetes.** We saw phase 3 data from Amylin's exenatide once-weekly, Takeda's alogliptin, Novo Nordisk's liraglutide, BMS/AZ's saxagliptin, and AtheroGenic's AGI-1067, as well as phase 2 data from a wide range of drugs including but not limited to Vivus's Qnexa, BMS/AZ's dapagliflozin, Roche's R1583 (taspoglutide), Intekrin's INT131, and Sanofi-Aventis's AVE0010. We also learned about a wide range of early-stage drugs and new classes in development. Last, we saw some very interesting data on currently marketed drugs, especially Symlin. Much of this data is presented above in Company Watch.

- **Overall, if there could be one theme, ADA 2008 was an incretin meeting.** There were many packed sessions about incretins, and Dr. Ralph DeFronzo (University of Texas, San Antonio) argued in his Banting Lecture that exenatide should be used as a frontline therapy (along with metformin and TZDs). There was so much talk about exenatide at the meeting that Dr. John Buse (University of North Carolina, Chapel Hill, NC) joked to his audience before presenting 52-week data for exenatide once-weekly that, "if you haven't heard of exenatide at this point in the meeting, I don't know, you should probably ask the meeting organizers for your money back." The ACCORD trial also added to the incretin momentum. In that trial, weight gain and hypoglycemia were proposed as explanations for the increased mortality observed in the intensive glucose control arm of the study. Neither is a side effect of incretin therapy. Interestingly, the ACCORD presenters showed a slide indicating that the small group of patients who used exenatide in the study had a significantly lower mortality rate than patients who used any other medication. Of course, the drug assignments in the study were not randomized and many factors may be at play here, but it is hypothesis-raising at the very least. Coinciding with the meeting, Novo Nordisk and Roche held investor conferences in which they each spoke about competing aggressively with first-mover Amylin/Lilly in the GLP-1 arena.

- **On the whole, ADA was negative for sulfonylureas as a class in our view.** Several speakers highlighted the importance of treating the underlying pathophysiology of diabetes, and explained that while sulfonylureas do lower blood glucose, they do not target a cause of diabetes and may not effectively slow the progression of disease. We believe that the continued pressure on sulfonylureas as a class (because of hypoglycemia, weight gain, and shorter duration of diabetes control) may drive incretin growth in the future. Price is the main advantage of SFUs at this time, and very important for uninsured or underinsured patients.

- **The ADA treatment algorithm was an item of some controversy at the meeting, as several speakers lamented that incretins are not currently part of the algorithm.** The most pointed criticism of the algorithm was during the Banting Lecture, when Dr. DeFronzo described the algorithm as a tool that "sets patients up to fail" by encouraging the use of sulfonylureas and not including incretins. Although the ADA has traditionally been conservative about adding new drugs to its algorithm, we believe that the organization should and will soon add incretins to the algorithm. For all of this controversy, one area that the ADA was spared criticism was in regards to A1c targets. Perhaps as a consequence of ACCORD, ADVANCE, and

the VADT, we no longer heard widespread calls for the ADA to lower its recommended A1c target from 7.0% to 6.5%. We think that it is unlikely that the ADA will modify its A1c goals in either direction anytime soon.

- **A common theme at the meeting is that diabetes should be treated earlier in its progression.** While this has been a theme raised in earlier ADA meetings by companies, we have never heard this so frequently in this meeting at so many different scientific presentations. For example, in the panel discussion, "Glycemic Control and Heart Disease - Implications for Clinical Practice" that followed the ACCORD presentation, several panelists proposed that ACCORD, ADVANCE, and the VADT failed to show a benefit of intensive glucose control on macrovascular complications because the patients had too high a rate of underlying conditions and too long a duration of diabetes (eight to ten years). They expressed optimism that earlier interventions during pre-diabetes might prevent diabetes and the associated increased risk for cardiovascular disease. Dr. DeFronzo made a related argument in his Banting address, arguing that beta-cells should be protected and insulin resistance should be reduced during pre-diabetes. He explained that people at the top tertile of normal glucose tolerance (NGT) have already lost 67% of their beta cell function, while people who progress to type 2 diabetes have lost about 80% of beta cell function. The ACT NOW (ACTos NOW for the Prevention of Diabetes) study, presented toward the end of ADA, also supported the effectiveness of early interventions in diabetes. In that study, pioglitazone reduced progression from pre-diabetes to diabetes by a remarkable 81% relative to placebo – the conversion rate to diabetes over the course of the study was 6.8% per year in the placebo group vs. 1.5% per year in the pioglitazone group.

- **The field of diabetes has converged with the fields of cardiology and inflammation.** Several speakers portrayed inflammation as an important driver of both cardiovascular disease and insulin resistance. Based on these presentations, we believe that there is growing interest in treating diabetes through reducing inflammation. At the meeting we learned more about a number of anti-inflammatory drugs in development for the treatment of diabetes, including AtheroGenics's AGI-1067, Hollis-Eden's Triolex, and Sirtris's SRT-501. Debate continued at the meeting about what effect the TZDs (Actos, Avandia), which reduce inflammation and insulin resistance, have on cardiovascular disease risk.

- **We also heard a lot at the meeting about the importance of individualizing treatment goals and therapy,** but we believe that any movement in this arena will butt heads with challenging physician economics. Individualization requires increased health care provider time, and the present reimbursement environment is actually causing health care providers to spend less time with patients. We do believe individualization of care is important – this plays into simpler drugs and devices gaining even more momentum – but we won't hold our breath for full individualization because at this stage, the reimbursement for it just isn't there.

- **Finally, on the topic of physician economics, we were pleased to present our own poster at ADA calling attention to a lack of interest in treating diabetes among medical school students.** Of the 524 medical students we surveyed last year, only three students expressed an interest in pursuing diabetes care. Difficulty in changing patient behavior, lack of procedures, and low compensation were frequently cited by students as reasons not to enter the field. These data suggest that without changes to our reimbursement structure, America's shortage of endocrinologists is likely to expand in the future. Our abstract is available on the ADA website (poster 864-P) "Who Will Manage American Patients with Diabetes in the Near Future?"

There were many goings-on at the exhibit hall at ADA – we give you some of our impressions below of the fast-paced activity there!

Exhibit Hall:

- **Abbott**: The FreeStyle Navigator, Abbott's recently approved CGM, was highlighted at the booth and this was great to see given all the momentum in the area. Reps were explaining to healthcare providers that it can be placed on the stomach or back of arm and one representative said, "unless you're on a mall shopping spree, it's probably not going to be ripped off of the arm." She was disappointed that the Navigator was not available to try at the booth. What's missing is an integrated insulin pump though the relationship with Smiths could fill this gap. The reps also spoke at length about the advantages of Freestyle Lite, explaining the no-coding benefit and the fact that patients can add blood to the test strip for a full 60 seconds - great if patients need to "juice" their fingers again or prick their fingers repeatedly for more blood. Giveaways included Rubik's cubes with diabetes graphics and pictures taken in front of a large cityscape of San Francisco. Perhaps the coolest booth feature was Team Type 1 cycling in front of a giant Navigator readout… some doctors and CDEs watched team type 1 for minutes upon minutes and we admit to being pretty mesmerized too!

- **Amylin**: Amylin had one of the most informative booths in the exhibit hall, lined with large backlit posters displaying clinical data. Approximately 75% of the booth was devoted to Byetta. One corner of the booth reviewed the compelling 32-week crossover head-to-head trial of Byetta vs. Lantus (known as the "Heine trial" in the business). Pointing through the poster, the company reps showed us that Byetta delivered comparable improvements in A1c relative to glargine, with less hypoglycemia. The reps left us with a copy of the original article describing this study, which was published in the November 2007 issue of the journal *Clinical Therapeutics*. The Symlin part of the booth featured a large poster showing that Symlin improves postprandial glucose control and glucose fluctuations throughout the day. Several booth panels highlighted the weight-loss benefits of Symlin and Byetta. Amylin also offered free health screening, and conveniently played a video about Byetta as visitors awaited their results. Giveaways included a flash drive with key literature and lots of memory (our favorite gift of the conference) and Byetta bags.

- **Animas**: Very impressive marketing as always. They prominently displayed a chart comparing their 2020 pump with Medtronic's pumps as well as the Animas Diabetes Management Software – "ezmanager max." In a "first," the software is both Mac- and PC-compatible, making it very user friendly. The cool graphics and new report detail in the software will make management simpler and easier for both the healthcare provider and patient. This is key, as Medtronic's CareLink software has up until now led the pack on software, which makes a major difference to healthcare providers – software is a big tool for them to see where and how patients can improve basal rates, insulin to carb ratios, insulin sensitivity factors, etc. We expect the booth to be even better at AADE as they'll have the Ping pump to show as well!

- **Archimedes**: Archimedes showcased its new algorithm in determining an individual's propensity to diabetes, cardiovascular disease, and many other diseases, which was highlighted on the ADA website as Diabetes PhD. The booth's representatives were very excited to demonstrate the simple web interface to passing attendees, though they were unfortunately stuck in a low traffic zone. The representatives showed off several papers discussing the algorithm that the program used, which solved thousands of equations simultaneously to achieve a 99% accuracy in predicting future risk. They plan to package the software and distribute it as a product capable of simulating possible healthcare policy changes as well as help insurance companies assess individual risk levels.

- **Arkray** (including Hypoguard): They had their current portfolio of products displayed with a special focus on the advanced products now available in the US from Japan such as the Glucocard X meter. The new PocketChem EZ meter with an easy-to-use two step method was prominently featured as well.

- **Bayer Diabetes Care**: The booth showcased a complete portfolio of products (Contour and Breeze 2) including Bayer's new insulin pump "linked" meter, the Contour Link (this is the product that links to the Medtronic Paradigm pump, and is marketed outside the US). The large booth had some good traffic and we got a thorough run-down of all of the new features of the new Bayer Contour meter including the two personalized meter settings – basic and advanced. The new Contour meter can be personalized so a patient can focus on the information that they care about. The basic setting offers users simplicity – they just have to insert the strip and test. The advanced mode allows users to access customizable features, such as a wide target range for high and low settings to fit individual management needs. The advanced mode also includes pre- and post-meal markers with programmable post-meal reminders and an expanded set of averages. Patients can view 7-, 14-, and 30-day averages in addition to 30-day pre- and post-meal averages. Finally, the new Contour will come in gray, purple, and green in addition to the traditional blue. The Contour will be available later this summer. Bayer has done a good job in expanding its portfolio with the new colors and features for more personalized diabetes management – it's amazing that colors were not really an option before LifeScan started the move with the UltraMini in 2006! We love the Bayer software, which the company is known for pioneering – upon downloading, one actually comes close to feeling that a CDE is in the room. Bayer also seems excited about the new lancing device positioned as easier, more reliable, and less painful – we look forward to trying this at AADE. A new ad campaign featuring "real people" was good to catch of glimpse of as well… this is running on TV now at http://66.207.218.87/bayersimplewins/.

- **Bio-Rad**: They displayed and tested folks using the new "in2it" A1c system. The in2it is designed for clinical practice application and quick turnaround of quantitative A1c values. Though not quite as fast or simple to use as consumer-based glucose products, this new CLIA waived system gives the clinician an easy way to monitor patient values without having to send samples out for analysis. We aren't sure of the "real-world" accuracy though the lab values were good.

- **Becton Dickinson**: BD impressed us immensely with its press representative, who was so knowledgeable and personable that he got our visiting team member excited about needles. He covered everything from the technology of making an ideal needle (polishing the needle, lubricating each layer, and cutting each tip with three bevels) to why BD needles are available in so many sizes: "because people with diabetes come in so many shapes and sizes." As usual, the BD exhibit was very well put together and seemed to have a very global team – we spoke to associates from the US, Latin America, Japan, Europe, and elsewhere. This was great since ADA was certainly a very international meeting, so BD benefited from having so many reps so clearly adept in so many languages. Practically speaking, we learned a lot about how BD syringes hurt less – in addition to what BD calls the fine point technology (above, the distinct edges), they also do electro-polishing on all syringes (this polishes the needle and removes blemishes and rough spots), and they also coat each needle with lubricant. Who knew! It really is a science. Also, as usual, they had all the good education pieces on hand – we feel strongly that with 44% of people with diabetes not at their glycemic target (totaling over 7 million people in the US alone), there is no question that patients and physicians need more help becoming comfortable with injections and they need more education for teaching patients to inject. We find that educators get this – whether at companies or at hospitals or independent practices or group practices – and we hope that along with high quality industry-sponsored education like BD's, more and more private

educators will have the opportunity to interact with physicians and patients to get them comfortable with taking large molecule drugs, whether insulin, incretins, or otherwise.

- **Centers for Medicare & Medicaid Services:** Though it is not that surprising to find the organization responsible for overlooking the nation's largest payer at this year's ADA, they found themselves in a relatively dark corner of the exhibit floor, focusing on promoting a recent policy change in adopting competitive bidding for their durable medical equipment, prosthetics, orthotics, and supplies. Referring to recent cost cutting attempts as mandated by the federal government, the representative stated the organization's hope in controlling future Medicare and Medicaid costs. He did not say anything when we urged a closer look at spending on treatments that would contribute to reduced long-term complications.

- **Confidant**: This company showcased a way of using cell phones to help manage glucose. The cell phone and web-based software connects patients to a wide array of tools including the patient's blood glucose monitors (Abbott's FreeStyle Lite was on display). We know cell phone technology and blood glucose technology move at different rates so we think combinations could continue to be challenging although boy someone is going to figure it out and we look so forward to that time for the sake of patients. iPhone apps, anyone?

- **DexCom**: The DexCom booth had a huge model of its CGM receiver that was difficult to walk past without stopping and staring. This is the meeting where DexCom formally launched the manual calibration feature and we must say this is a feature that is fantastic for users to have as it represents less hassle. We were struck by the extent to which the representatives at the booth were glad to talk about the science of diabetes. They spoke to us at length about glycemic variability and we were very impressed with their knowledge and judgment shown. They also characterized the SEVEN as having "best in class" ability to detect lows; we think that detection of hypoglycemia and hyperglycemia is really where the money is in CGM, and regardless of which CGM actually is most accurate in hypoglycemia we think that it is smart of the company to speak about accurate readings on the low end. DexCom also discussed plans to integrate with Animas and OmniPod in 2009. We admired the "sensors R us" approach and the ease of use for the SEVEN demonstrated throughout the booth.

- **Diamyd**: This is the first potential preventative vaccine for diabetes that has shown statistically significant preservations in insulin production for recent-onset type 1 diabetes patients. The phase 3 trials have started in children and young adults aged 10 to 20 years old. This was a very small booth on a part of the floor with very low traffic, yet there were still many physicians visiting the booth.

- **Duke Medicine**: With only one representative and a small booth, it did not seem that Duke Medicine was expecting much traffic, although their free waist circumference measurement device and carbohydrate counting book were good to see. A lifestyle clinic associated with Duke University, they run a rigorous four-week program for patients hoping to lose and keep off approximately 5% of their body weight. Working intimately with patients on exercise and diet, they attempt to instill permanent lifestyle changes to encourage sustained health results. However, such personalized training comes with quite the price tag, costing around $8,000 per patient, making the majority of participants "very experienced dieters" within a higher income bracket who see the clinic as their last resort in adopting a new life.

- **Eli Lilly**: Eli Lilly's booth was one of the largest booths in the exhibit hall, although it was not as popular relative to other booths of its size. Products that were being promoted included Byetta (exenatide), glucagon, Lispro, and Humalog, as well as two products that are not specifically for people with diabetes: Cymbalta and Cialis. We were surprised to see what a small percentage of

the booth was dedicated to Byetta – only about 1/8 – yet this was not surprisingly the most popular part of the both – even given that Amylin had major Byetta features at its booth. The exhibit featured several videos on exercise and erectile dysfunction playing simultaneously on large TV screens. We do not remember seeing Cialis promotions at previous ADAs, and we wonder if the change in part reflects Eli Lilly's new co-marketing pact with Amylin in which Cialis has been more closely integrated into the diabetes portfolio (erectile dysfunction is a common comorbidity of diabetes). Giveaways included Byetta and Humalog bags, laser pens, and USB hubs (cool points), as well as a video about lifestyle management for patients. Frozen yogurt as usual was served.

- **Generex**: The representatives at Generex spoke about their insulin in development that is absorbed through the throat and mouth (buccal mucosa) rather than the lungs. We were impressed by the small size of the inhaler, which was comparable to an asthma inhaler although we remain negative about potential uptake. Though the representatives claimed that the product showed good glucose control and widespread use in India and Ecuador where it is currently approved, they offered little clinical data and simply said that it was currently in phase 3 trials in the United States.

- **Home Diagnostics**: The representative showed the TrueTrack blood glucose monitoring system and Sidekick blood glucose monitoring system. The representative was especially proud of the test strips, which she said "were half the cost of the competition." They were designed with quad electrodes, a special hydrophilic technology. The strips were promoted as the "cheapest on the market," which competitors took issue with. An updated version of the Sidekick is expected to receive FDA clearance in six months.

- **Intuity Medical**: This company displayed but did not demonstrate the "OnQ" integrated blood glucose monitoring meter – it looked very cool as we got to see it in a corner. The meter features full integration of the lancing device, lancets, test strips, data management, and meter into one device. We liked the form factor and think should be a hit with users when it becomes available in the future. The "OnQ" is a new solution for the age-old problem of how to simplify testing and all the ancillary stuff patients need to carry around in order to test. Though not alone is this approach, Intuity seem to be in the lead to commercialization ahead of Abbott, J&J, Pelikan, Roche, and others. We understand that this is an area that has been in development for some time, but past models from other players have failed to gain commercial success. Cost of goods sold will be the key commercial question – from a user perspective we think there are a number of patient groups who all else equal are eager to "less stuff" to cart around. The young and old will clearly benefit and this would be an excellent addition to any portfolio, assuming the economics work. …

- **Insulet**: Heavy booth traffic here and we loved the new larger-than-life body images with the Pod on a variety of locations… the abdomen, back, arm, and even leg. Got it – there's no arguing that no tubing provides greater flexibility. The booth allowed visitors to try on an OmniPod with saline – a very good opportunity to see the power of the automated insertion technology. Although there were no changes to the OmniPod to report for this ADA, there was lots of buzz about what's next in Insulet's portfolio, including a look at the integrated CGM System and a smaller Pod. We got to see the new Pod, which was way beyond a prototype – we think it will have big-time appeal, as it is considerably smaller but is meant to do all the same things… get this approved!

- **Insulin for Life:** Focusing on distributing insulin and diabetes test strips, their largely grassroots campaign has attracted the attention of the World Health Organization, which has made them a first responder to deal with future global crises such as the tsunami in Sri Lanka or

Hurricane Katrina in New Orleans. Relying on private donations, especially from Europe and specifically Germany, they were hoping to gain additional exposure in the United States and other first world countries.

- **J&J Diabetes**: This booth had great energy surrounding the OneTouch Ultra and OneTouch UltraMini. The representative there made a case for LifeScan test strips being the most inexpensive on the market because LifeScan is covered under many insurance plans. There were also so many representatives at the booth that it always seemed to be lively. They were showing the Medtronic insulin pump-linked meter "Ultra Link," which should help keep them at the front of the US glucose testing market – very innovative agreement and we're impressed how many pumpers they have engaged. The newly formed Johnson & Johnson Diabetes Institute took front stage as a key new diabetes education and training resource and we were blown away by the video – class act, highlighting Dr. Francine Kaufman and Dr. Nancy Bohannon, among other noteworthy endocrinologists. J&J does an outstanding job in our view in developing and delivering services (like the recent Children With Diabetes acquisition) to support their core diabetes businesses, LifeScan and Animas. We continue to love the UltraMini, the tiny meter that is clearly a hit with healthcare professionals – and patients, in blue, pink, green, and black.

- **Merck**: Merck dominated a large part of the ADA exhibit floor, covering nearly an entire row with its main booth and multiple side booths. There was extensive interest in Januvia and Janumet, and somewhat less in Merck's cholesterol lowering and cardiovascular protection drugs, as more is known about those. Merck offered free smoothies, health screenings, and a personalized BMI kit, which a lot of visitors were waiting in line for, surrounded by posters promoting the Januvia franchise.

- **Nestlé**: Though Nestlé's booth was small considering the corporation's influence in the distribution of the world's manufactured foodstuffs, it still generated a good amount of interest, primarily thanks to the booth's ideal placement at the intersection of two very busy aisles and free samples of low-glucose high-protein energy drinks. The representatives expressed Nestlé's dedication in becoming the world's largest medical food vendor, and emphasized their products' focus on improving overall health rather than targeting any specific disease such as diabetes. They also were incredibly proud that their energy drink was recently used in a clinical trial that showed superior glucose control in patients that drank it at least twice a day.

- **New Balance**: "Never underestimate the effects of a good pair of shoes." New Balance has certainly capitalized on that sentiment. Though they were tucked away in the corner of the exhibit hall, the New Balance station garnered plenty of attention for their shoes focused on promoting diabetes care in affected patients. With features targeted toward diabetes patients such as specific size/width ratios, leather linings, and memory foam top covers, they were hoping to tap into the growing need for highly specialized diabetes products. The representative stated that they were "all about the fit" and that they were really focusing on precision fitting for their customers.

- **Novo Nordisk**: Undoubtedly, this was one of the most appealing and thoughtfully planned booths at this year's ADA – and the busiest! Nintendo Wii consoles were set up with controllers that resembled Novo Nordisk insulin pens, digital jump ropes were awarded, and there was an elliptical trainer that would squeeze fruit juice when it was stepped upon. Incredibly well put together, virtually every aspect of the booth was educational as well as engaging. Medical literature was given out on the second story of the booth – it looked oh so relaxing up there! The booth downstairs highlighted Novolog, forthcoming liraglutide (which got a lot of attention due to news out just before the meeting on a head-to-head trial vs. Byetta, LEAD-6), and long acting basal insulin Levemir.

- **Pelikan**: The "PelikanSun" electronic lancing device was the sole featured product and speculation continued on the integration of a glucose monitoring system with the automated lancing feature.
- **Pfizer**: This was a significantly downsized booth from Pfizer's Exubera days. The company was giving out personalized pen stands. The booth was mostly devoted to the promotion of Lyrica.
- **Roche**: While most of Roche's scientific sessions at ADA were on the drug side, their ADA exhibit was all about devices – understandable because all of their diabetes drugs are development stage. Most of the relatively small booth focused on Accu-Chek Aviva.
- **Sanofi-Aventis:** Sanofi-Aventis had two large booths. The endocannabinoid booth proudly displayed a 3D theater complete with plush stools and viewing glasses, displaying an intricately designed video on the mechanism of endocannabinoid action. We were surprised to see such a focus on educating patients about CB-1R inhibition (and, by extension, the mechanism of action of rimonabant), given all of the concerns about the drug's safety and the fact that it is not approved in the US. When asked about new offerings, the reps briefly mentioned the buzz around the new Apidra pen, and also the new GLP-1 mimetic under development called AVE0010, but declined to give any specifics. Overall the booth was rather underwhelming and seemed to lack real direction in terms of products, and we got the impression that it was mostly staffed by contractors. In contrast, Sanofi-Aventis' insulin booth was well staffed with company sales reps and was quite popular, with many visitors stopping to hear about the Lantus SoloStar pen. Apidra was also advertised.
- **Takeda**: Takeda aggressively marketed alogliptin, the once-daily DPP-4 inhibitor that was filed in the US in early January, at its booth this year. The lack of hypoglycemia for patients on alogliptin and the comparable rates of hypoglycemia for controls were emphasized. Visitors were immediately asked to scan their badges for more e-mail information on alogliptin. The booth had a lot of energy, perhaps because of the new presence of alogliptin. The giveaway was a mouse pad that was scanned with attendees' pictures and the Takeda diabetes "characters." Actos, of course, was also a big feature here.
- **Tethys**: With a new algorithm attempting to assess the risk of obese patients developing diabetes, the representatives at Tethys were very excited to promote their PreDx product. For a new entrant in the ADA scene, Tethys had a surprisingly large and spacious booth surrounded by plasma screen TVs marketing their product. Their test measures key proteins in the patient's blood and has comparable accuracy to the oral glucose test; representatives said they hope that it will help physicians predict a patient's propensity for developing diabetes and thus allow for earlier and more aggressive intervention. Furthermore, the representatives explained that the test is able to distinguish between low- and high-risk individuals with BMI greater than 25. The latter are four times more likely to develop diabetes even though they comprise less than 10% of this subpopulation. Interest was good…
- **Tolerx**: Tolerx had a small booth aimed at recruiting investigators and type 1 diabetes patients for an upcoming phase 3 clinical trial (DEFEND) of its anti-CD3 monoclonal antibody, otelixizumab. The reps explained to us that results published in 2005 in the *New England Journal of Medicine* found that a six-day treatment with otelixizumab in recently diagnosed patients with type 1 diabetes preserved pancreatic beta cells and decreased the dose of insulin needed to control diabetes. Tolerx currently has two sites for the phase 3 trial up and running in the United States and plans on eventually including 120 sites and 240 participants in the study. Tolerx is recruiting patients aged 18 to 35 who were diagnosed with type 1 diabetes within the past 90 days. A total of 160 subjects will receive a daily two-hour IV infusion of otelixizumab for eight

days, followed by a two-year follow-up period in which they will be compared to 80 subjects that received the placebo. Although the Tolerx booth was small and there were was not a large crowd, there was a lot of enthusiasm among the representatives that this novel therapy will reduce the autoimmune attack on beta cells in type 1 diabetes patients.

- **Veralight**: Veralight has an exciting device in development for non-invasively screening for type 2 diabetes and pre-diabetes. We huddled up against a crowd to get a demonstration of the product, which uses fluorescent spectroscopy to measure advanced glycation endproducts in a patient's forearm. The eventual goal is to create a diagnostic tool for type 2 diabetes and pre-diabetes. Though not yet approved for commercialization, the product could offer a tool for clinicians for asymptomatic diabetes screening, though our understanding is that blood glucose tests for diagnosing and monitoring diabetes are unlikely to be replaced in the future, due to their accuracy and routine nature.

- **WaveSense**: The team at the WaveSense booth was incredibly well-informed and gave great presentations on the various meters. The booth was large for a meter company their size – they're obviously thinking big and the traffic was impressive, due in part, we're sure, to some star power they had with noted diabetes blogger Amy Tenderich. We were psyched to pick up a meter to test drive in a future issue of diaTribe (www.diaTribe.us). Their new and expanded portfolio is at the leading edge and we look forward to more coverage news.

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

5. In the News I: FDA Advisory Panel Recommends Cardiovascular Outcomes Trial Requirement

In light of the controversy about the validity of A1c as a surrogate marker for cardiovascular risk, the FDA held an advisory panel meeting on July 1-2, 2008, to discuss cardiovascular risk in new diabetes drugs. After a day of presentations from a variety of experts and a full day of deliberation, the advisory panel voted 14-2 in favor of requiring all new type 2 diabetes drugs to demonstrate cardiovascular safety in a hard outcomes clinical trial, or by other means, even if no concerning cardiovascular signal is observed in phase 2/3. The vote reflected a general consensus among the panelists that the FDA currently does not have enough data to rule out cardiovascular harm with new diabetes drugs. The vote is somewhat of a paradigm shift from the way diabetes drugs are currently approved; the FDA currently only requests long-term cardiovascular trials for a drug when there is a concerning cardiovascular safety signal in phase 2/3. We believe that this decision will adversely affect diabetes drug development, although the degree largely depends on what version of the many proposals discussed is eventually implemented by the FDA.

Below is a discussion of the various proposals, our opinion of the decision, an assessment of possible implications for diabetes drug development, and other key takeaways.

- **Dr. Steven Nissen (Cleveland Clinic) may have a rocky history with the FDA Endocrinologic and Metabolic Drugs Advisory Committee, but his presentation at this meeting seemed to dazzle the committee.** Dr. Nissen suggested that the FDA require a pre-approval cardiovascular endpoint study to ensure that a drug does not cause significant cardiovascular harm above a certain level, followed by a long-term post-marketing study. However, he argued that the FDA has little power to enforce post-marketing trials and therefore a smaller and shorter pre-approval study is necessary. His arguments in favor of a cardiovascular outcomes trial seemed to sway the panel much more than other presentations from Dr. David Nathan (Harvard Medical School), Dr. Robert Ratner, M.D. (Georgetown University Medical

School) and Dr. Hertzel Gerstein, M.D. (McMaster University, Ontario, Canada), all of whom either directly or indirectly opposed a cardiovascular outcomes trial.

- **The panelists agreed that the FDA should use an independent blinded adjudication committee to monitor cardiovascular events for diabetes drugs.** The panelists expressed hope that this would lead to the standardization of cardiovascular adverse event reporting and other aspects of clinical trial design, in order to provide better information to the FDA. The panelists highlighted that an adjudication committee with clearer standards for reporting cardiovascular events and other adverse events would allow better analyses of data without impeding drug development.

- **If phase 2/3 trials were better standardized, panelists expressed hope that meta-analysis of safety data from the phase 2/3 trials would be more revealing regarding cardiovascular risk and unexpected complications.** Several members of the panel underscored that the lack of standardization in the rosiglitazone (Avandia) phase 2/3 clinical trials made it difficult to assess that drug's effects on cardiovascular risk.

- **The panelists also generally agreed that the FDA should require more robust phase 2 and phase 3 clinical trials, because they felt that the current safety database is inadequate.** The panelists justified their position by pointing out that mortality and complication rates for people with diabetes have fallen over the past 10-20 years, and therefore the safety hurdle for new drugs should be increased to ensure that the new drug is not doing more harm than good. The committee produced no specific recommendations, aside from several presenter comments noting that phase 2/3 clinical trials should include more high-risk patients. The consensus about a need for larger phase 2/3 clinical trials preceded the panel's discussion about a cardiovascular safety study; presumably a cardiovascular safety study would fulfill the panel's desire for more robust pre-approval clinical data.

- **The panelists unanimously agreed that diabetes drugs should not be required to show cardiovascular benefit.** Echoing statements made by Dr. David Nathan in his presentation on day 1 of the conference, panelists mentioned that diabetes and cardiovascular disease are truly separate disorders. Therefore, they believed that it would be appropriate to approve a diabetes drug that does not cause cardiovascular benefit but is effective at lowering A1c, so long as the drug is safe. Several panelists underscored that cardiovascular benefit has not been demonstrated for any of the currently available therapies (except possibly metformin monotherapy in the UKPDS), and therefore it would be unreasonable to expect all new drugs to produce cardiovascular benefit.

- **There was a near-consensus among the panel members that the FDA does not currently have enough data to rule out cardiovascular harm with new drugs for type 2 diabetes – drugs for type 1 diabetes were discussed by this panel.** Most panelists said that a cardiovascular outcomes clinical trial should therefore be required for all new drugs, including new drugs without a concerning cardiovascular safety signal in phase 2/3. The vote in favor of a cardiovascular study requirement was 14-2; dissenters included a pediatric endocrinologist (Dr. Eric Felner) and, notably, the only patient advocate on the panel (Rebecca Killion, interviewed in this issue of DCU – see page 9).

- **Panelists agreed that the cardiovascular safety study requirement should apply to all drugs within a class, not only first-in-class drugs.** Panelists were apparently impressed by a slide presented by Dr. Nissen demonstrating the large differences in gene activation by the currently and formerly approved PPARs. Dr. Nissen's argument was that within the TZD class, every drug is truly unique and may have a different cardiovascular effect. We believe that the TZD

class is somewhat unique in this respect, and given the mechanisms involved, the idea that all GLP-1s or DPP-4 or SGLT2 inhibitors may carry different cardiovascular risks is misguided. The cardiovascular study requirement is likely to eventually appear ridiculous when the sixth DPP-4 inhibitor comes to the FDA advisory panel, with cardiovascular data from 2,500 people that look super-imposable to every other five approved DPP-4 inhibitor.

- **There was less of a consensus about what kinds of cardiovascular studies the FDA should require, and what level of potential cardiovascular risk is acceptable for diabetes drug approval.** Panelists were divided about whether the cardiovascular study should be conducted pre-approval or post-approval, or some type of "hybrid" approach involving a pre-approval "screening study" followed by a "confirmatory trial." One proposal by Dr. Thomas Fleming that was generally well received was that drugs should be required to rule out with 95% confidence a cardiovascular hazard ratio of 1.8 or above (point estimate of ~1.5) in a single randomized pre-approval trial. This screening trial would require about 125 cardiovascular events. Assuming a population with a baseline 2% per year rate of cardiovascular disease/myocardial infarction/stroke, this would translate to about 2,500 patients (1,250 in study arm, 1,250 in control arm) followed for approximately 2.5 years. This trial would enable drugs to show absence of cardiovascular toxicity, or to show cardiovascular benefit. If this screening trial requirement were implemented, it would prevent six of seven drugs with a hazard ratio of 1.5 from being approved. The screening trial could then be followed by a confirmatory trial, to rule out a lower hazard ratio of about 1.333 (such a trial might require approximately 5,000 participants followed for five years).

- **The FDA received less clarity from the advisory panel than it had likely expected or hoped for.** The advisory panel was expected to provide a yes/no vote to the following question: "For those drugs or biologics without [a concerning cardiovascular safety signal], should there be a requirement to conduct a long-term cardiovascular trial?" However, panelists demanded more wiggle room, and the question was eventually reworded before the final vote to say: "For those drugs or biologics without a concerning cardiovascular signal, should there be a requirement for a long-term cardiovascular clinical trial *or to provide equivalent evidence from other sources to rule out an unacceptable cardiovascular risk*?" Therefore, at face value the 14-2 vote in favor of the above statement does not necessitate a cardiovascular safety study. Nonetheless, it is hard to imagine that the FDA will be able to rule out "an unacceptable cardiovascular risk," even for a drug that produces cardiovascular benefit, without greatly expanding the clinical trial requirements.

- **Panelists generally agreed that all approved non-generic drugs should undergo a similar cardiovascular safety assessment.** The panelists suggested that it would be inconsistent not to require approved agents to fulfill the same cardiovascular hurdle as new drugs. In our view, it is inconsistent to allow generic drugs to go untested – although admittedly it is unclear who would pay for such clinical trials of generic drugs. The only class of drug that has demonstrated cardiovascular toxicity is the sulfonylureas, and they would be excluded from such a clinical trial requirement.

- **The devil is in the details, and to get the details we will need to wait for the FDA's response to the panel's recommendations.** Although it is possible that the FDA will reject the panel's suggestion of a cardiovascular safety study requirement entirely, we believe this is highly unlikely given the 14-2 vote count. That the agency held this advisory meeting in the first place and invited Dr. Steven Nissen to present suggests that the agency is very willing to revise its requirements in this regard.

- **We believe that the most likely outcome will be a hybrid pre-approval screening study/confirmatory trial requirement.** This could delay the approval of drugs slightly or significantly as the screening study would likely take at least 2 years or more to complete. Panelists indicated that two or three years would likely be the minimum amount of time required to see a clear cardiovascular safety signal. This hybrid trial system could be designed as a five-year (or so) study beginning pre-approval and ending post-approval, with an interim analysis at two years, scheduled to occur at the time that the drug is filed. Alternatively, this hybrid system could consist of a shorter pre-approval trial, followed by a separate larger post-approval trial for any drug trending non-significantly in the wrong direction in the pre-approval trial. We expect the trials to run somewhere from 2,500 patients to 5,000 patients with a duration of two to five years. Approved drugs will likely have to undergo a post-marketing study of similar scale.
- **On the surface, the proposal for a cardiovascular safety study requirement is negative for all companies in the diabetes space, but companies may be affected very unequally.** The clinical trials could demonstrate cardiovascular benefit for some classes of drugs, greatly expanding their use as other drugs fail to show such benefit in FDA-mandated clinical trials. Specifically, there is reason to believe that GLP-1s will be shown to bestow a cardiovascular benefit, and this could greatly expand the GLP-1 class. We think that Amylin and Novo Nordisk should be thinking about designing a PROactive-like study for Byetta and liraglutide, regardless of the FDA's final decision. The SGLT2s could also prove to have cardiovascular benefits, given their similar association with weight loss. The requirement for a cardiovascular safety study would likely modestly or significantly delay the development of drugs that are currently in earlier stages of development. We believe that it is likely that companies with drugs in phase 3 may instead be required to conduct a post-approval cardiovascular outcomes study.

— by Melissa Tjota and Mark Yarchoan

6. In the News II: Medtronic Discuses Low-Glucose Suspension Feature

On June 10th, Medtronic discussed with Close Concerns the development of a "low-glucose suspend" (LGS) feature for its existing Paradigm platform (insulin pump/continuous glucose monitoring [CGM] system) of which the 522/722 is the latest product. The LGS feature represents a first, small step toward an artificial pancreas – automatic shutoff of insulin during periods of untreated hypoglycemia. The technology, using a new sensor algorithm, automatically halts insulin delivery when the user's blood sugar reaches a user-defined level, thereby reducing the risk of severe hypoglycemia. This is, to our knowledge, the first time that pumps and CGM will interact using a truly automated feedback loop in a potentially lifesaving fashion.

The LGS feature has been tested in a 30-person user-evaluation study in the UK, and although analysis is still ongoing, Medtronic executives – specifically, CGM guru Dr. John Mastrototaro, PhD, VP Global Medical, Scientific, and Health Affairs and Brad Enegren, VP of Research & Development – were bullish enough about this product that they spoke to us about it. Dr. Mastrototaro detailed the workings of the LGS feature, improvements to the sensor algorithm, and the regulatory path for this innovation. As we had learned late last year when we first reported on the "auto-off" shutoff from the Global Diabetes conference in Columbus, Ohio, the tests are taking place in the UK because the regulatory path is easier there. It took some time to wrap our heads around this issue: a technology that increases safety is better to test overseas because things are too slow in the US? At a time when the number of intensively

managed patients (especially those hypoglycemic unaware) is at record levels, the fact that we have to wait – oh, for safety reasons – dismays us.

- **The low glucose suspend (LGS) feature suspends basal insulin infusion for two hours if the low-glucose suspend alarm is activated and the user does not respond to it.** Currently, users of the Medtronic Paradigm Real-Time integrated insulin pump and CGM have adjustable Hi/Lo blood glucose thresholds. The LGS feature adds an additional adjustable threshold that is set below the Lo alarm threshold. If a user's measured glucose level drops below the Lo threshold, an alarm goes off to alert him/her. If the user does not respond to the alarm and glucose levels drop to the LGS threshold, another alarm goes off followed by a two-hour halt in insulin infusion. The range for the LGS threshold is 40-110 mg/dl[1]; notably, there is a mechanism in place that prevents for safety reasons the LGS threshold from being set above the Lo threshold.

- **After the two hours have elapsed, insulin infusion begins again regardless of user interaction (i.e. whether or not the low has been treated or the alarm has been switched off).** The goal is to prevent diabetic ketoacidosis (DKA) – a condition characterized by extreme hyperglycemia that can result in a diabetic coma. While the new feature clearly won't be able to fix every dosing error, we believe it will be useful in fixing a number of things that prompt low glucose, including microdosing errors (e.g. 0.5 – a few units errors), mealtime delivery errors, early morning hyperglycemia (i.e., errors in dosing in response to the dawn phenomenon), or temporary hormone-related hyperglycemia. It could also be particularly useful in catching hypoglycemia resulting from exercise. Professor John Pickup of Guy's Hospital in London, an investigator in the LGS user evaluation study, suggests that patients on insulin pumps still experiencing marked hypoglycemia be the first to trial LGS equipped pumps.

- **As with any alarm based on a CGM reading, users are advised to perform a confirmatory fingerstick test since CGM is not indicated as a basis for therapeutic decisions.** The user may choose to turn off the auto-suspend (maintaining insulin infusion) or allow auto-suspend to occur for two hours during which time he/she should treat the low while monitoring for hyperglycemia. Currently, a simple on/off toggle controls insulin suspension. Medtronic notes that this feature may change to require additional steps depending on user practice in evaluation studies. From our understanding, it takes about 15-20 minutes from the initiation of auto-shutoff of insulin infusion to see any effect on glucose levels – that is because insulin takes roughly 15-20 minutes after infusion to cause cells to take up glucose. If a user responds to the initial Lo threshold alarm, the LGS feature does not kick in.

- **On the regulatory front, Medtronic appears to be working hard to build a strong case for the FDA.** Thus far we know of the single 30 subject, six week, six center user-evaluation study in the UK. While no formal user data has been released, we are optimistic about the rough findings. We assume this study was performed in Europe for the following reasons: 1) the approval process is typically shorter in Europe, so it makes sense to tackle the "easier" hurdle first, and 2) the current challenging regulatory environment in the US –in our view, the FDA's stringent demands are effectively forcing American companies to initially go abroad with products that American consumers clearly need and want. Dr. Mastrototaro noted that Medtronic was currently negotiating with the FDA about the clinical trials required for US approval. He expressed his hope that an agreement would be reached with the European regulatory authorities regarding the clinical trials at the end of calendar year 2008. He noted that experimental

[1] We think the upper limit of this range could be on the high side – considering the "normal" fasting plasma glucose is below 100 mg/dl (ADA). Shutting off basal infusion with a glucose level 100 mg/dl may not be a good idea though we imagine a wide range is just in the interest of having a broad continuum available for patients.

protocols were expected to be completed - sites and investigators identified - to allow access to the LGS feature in countries recognizing the CE mark by mid-2009. While we would guess 2010 for the availability of this feature in the US, Medtronic spoke cautiously about the domestic regulatory process, and we should point out that Dr. Mastrototaro preferred not to give a specific timeline.

- **Some of the scientific and technical questions raised in the 30-day trial by the investigators during the study revolved around the duration of auto-suspend time – is two hours long enough?** From our conversation, we understood that the two-hour auto-suspend time, the period between the LGS alarm and auto-shutoff, was selected because it seemed "safe." Although some would want an "auto-off" to last longer, others would be more worried about DKA. Two hours appears a safe - albeit conservative - compromise between simultaneously preventing DKA and severe hypoglycemia. Overall, we understand the feature was positively received in this initial testing in the UK, and the investigators were positive about what they saw as the first step in closing the loop.

- **In a follow-up conversation we had with Brad Enegren, he noted that treatment of hypoglycemia was a logical first step towards the closed loop.** He suggested other steps in the process, including hyperglycemia, nighttime closed loop, then daytime closed loop during meals. The last point is the largest hurdle and requires the most refined algorithms. He said that while these steps individually may appear to be small, *en masse* they would have a significant impact. Additionally, smaller steps may be easier for users to accept, and they may be easier to gain approval from regulators.

- **Enegren indicated that the insulin companies would be instrumental in addressing the multiple questions on lag time where the closed loop is concerned.** It makes sense to think that while the CGM companies keep improving sensor technology and decreasing lag between blood glucose and interstitial fluid, faster acting insulins would approach the lag question from the other end – more physiologic insulin delivery.

- **A separate correspondence with closed-loop researchers Dr. Bruce Buckingham and Jennifer Block, CDE, of Stanford University, reinforced the potential value of LGS for those with severe hypoglycemia.** Dr. Buckingham noted that in most cases seizures do not occur for two to four hours after the sensor glucose has been below 60 mg/dl. Thus, the LGS threshold alarm could significantly decrease the risk of a nocturnal seizure. Block stated that "There is much we all have to learn about the ideal threshold and duration of basal suspension." On a slightly cautionary note, she emphasized, "While the best method to treat low blood sugar is the consumption of fast acting carbohydrates, the reduction or suspension of basal insulin with guidance from a healthcare team may be used to prevent a low." She added that basal suspension should be thought of as a last resort and even then should only be allowed for a short duration. Speaking from both a patient and educator perspective, she emphasized the need for further advances in the integration of CGM and insulin delivery, calling for similar trials in the US and lauding the work of all the CGM companies, investigators, and organizations in the field: "For those of us who live everyday with diabetes, advances like this can not come fast enough." The Stanford team eagerly awaits the opportunity to review the formal results of the UK trials.

- **We could see any pump user wanting this feature, but it will likely be sought after for use by children, intensively managed patients, and patients suffering from**

hypoglycemia unawareness. In addition, patients who often sleep through the existing alarm functions on the Paradigm models could also benefit[2].

- **Ultimately, we hope that the FDA recognizes the significance of this technology and will work closely with Medtronic in establishing clear and realistic guidelines for testing and approval in the US.** Patients obviously care about safety first, but they do not want vital products held hostage to unreasonable bureaucratic fears. That insulin pumps and sensors have come this far is a testament to the commitment of medical device companies like Medtronic as well as organizations like the JDRF, which has made closing the loop one of its central goals. Let us hope that the LGS feature, with the assistance of all concerned, moves us one step closer to managing diabetes – and that it moves quickly.

— by Kaku Armah, Kelly Close, and Jim Hirsch

7. In the News III: New CDC Report on Diabetes Prevalence and Associated Costs

The report, released on June 24, updates the diabetes statistics compiled by the CDC. Since the CDC last reported on diabetes stats in 2005, this update is useful in considering recent diabetes trends and clinical and commercial implications. There are several new important pieces of data: 1) the estimated number with diagnosed and undiagnosed diabetes nationwide has risen to 24 million; 2) the number of people with prediabetes is now estimated at 57 million, up from 41 million in 2000. As we reported earlier this year, the estimate of the total cost of diabetes has risen to $174 billion, with $116 billion in direct costs. From our view, the most unsettling factor is the cost of complications, estimated at $58 billion. The dramatic increase in complications (the cost of complications in 2002 was only $25 billion) reinforces our view that spending on complications in the US has become truly alarming. Our private correspondence with authors indicates that there was no change in the methodology used to estimate these costs. On a more positive note, although the costs of diabetes in the US continues to rise at a fast rate, people diagnosed with diabetes are living longer: despite an increasing prevalence of the disease, the annual death rate has stayed almost constant since 2002 (69,300 then and 73,500 now)

- **In 2007, 1.6 million new cases of diabetes were diagnosed in patients over 20, compared with 1.5 million in 2005 and 1.3 million in 2002.** In all three years analyzed, the greatest numbers of cases were diagnosed in the 40-59 age group.
- **There were significant changes to diabetes treatment regimens from 2001-2003 to 2004-2006.** There was a small decrease in the use of insulin monotherapy (16% to 14% of patients) over this period, compensated for by a small increase in the use of insulin in combination with other therapy (12% to 13%) and patients on no therapy (12% to 13%). These differences might even be due to statistical variation, especially because the numbers are reported only as integers.
- **The risk of death for those with diabetes is about twice that for unaffected people of a similar age**. This difference in risk has stayed constant since at least 2005.

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[2] Importantly, it should also help correct the problem of low inaudible alarms sometimes experienced by those using the current CGM in the Paradigm models – there are those users who can sleep through three hours of the "siren" alarm function, believe it or not! "Not everyone lives with someone else to watch out for them and they may not necessarily be hypo-unaware but just not light sleepers…" said one Paradigm pump user with whom we recently spoke.

- **The rate of diabetes complications has been relatively stable over the past few years.** Although there have been small increases in the rate of nephropathy from 2002 to 2004, the rate of diabetes—related amputations has decreased. Data for other complications such as neuropathy and retinopathy remained constant. As we pointed out above, despite the near-constant rate of complications, the cost associated with them has been skyrocketing. Some of this can be attributed to the increase in the absolute number of patients with complications over the years, as well as increasing cost of treating each complication, and the length of time patients have complications – we'll be trying to research this disparity in the coming weeks.

— by Kaku Armah and Brendan Milliner

8. In the News IV: ACCORD, ADVANCE, and the VADT

ACCORD, ADVANCE, and the VADT are three large clinical trials whose results were presented at this year's ADA. Each of the trials investigated the relationship between intensive glucose management and cardiovascular outcomes. The overall results were a net loss for intensive glucose management, as none of the trials showed a link between intensive management and lower macrovascular outcomes. Since February, when we learned that the intensive glucose management arm of ACCORD was being discontinued because of increased mortality, the ACCORD group has performed a range of analyses to track down the cause – and have yet to discover anything of significance. We fear that the reporting of these trials in the mainstream media may cause more rather than fewer shoulder shrugs among the primary care doctors who treat patients with diabetes and many of the patients themselves (note the June 7, 2008, New York Times *article titled "Tight Rein on Blood Glucose Has No Heart Benefits"). Below are more details about the three trials and a review of their potential implications.*

- **ADVANCE was a huge 11,000-person, international five-year trial that randomized patients to conventional or intensive glucose control (mean A1c values were 7.3% and 6.5%, respectively, at the trial close, from a baseline of 7.5%).** All patients in the intensive arm received sulfonylurea (gliclazide modified release), and patients in both arms received a range of other oral drugs (primarily non-TZDs) and insulin (basal and mealtime) as needed to lower glucose. There was a greater emphasis on lifestyle management in the intensive arm, which we believe included more physician visits and presumably better diabetes education – this was likely one of the reasons for the better results in the intensive arm, though disappointingly, the impact of education was not addressed in the reporting or discussion. The researchers found that intensive glucose control reduced microvascular disease outcomes (retinopathy and nephropathy) by 14% (p=0.01), but did not have a statistically significant effect on macrovascular outcomes (heart attack, stroke, or cardiovascular death).
- **ACCORD randomized 10,251 subjects to intensive or standard glucose arms targeting A1c goals of 6.0% or 7.0-7.9%, respectively.** As with ADVANCE, a wide variety of diabetes treatments were used, and treatment paradigms were left to the physician discretion. However, as reported previously, the study's data safety monitoring board discontinued the intensive glucose arm of the study after it found that the intensive glucose arm had 22% more deaths than the standard treatment arm. Subsequent sub-group analysis found that the increase in mortality could not be attributed to any single diabetes treatment. Breaking down all the outcomes, there was a general trend toward increased cardiovascular death, arrhythmia, and congestive heart failure with intensive therapy, although there were fewer incidences of non-fatal MI in the intensive group. Notably, however, a concurrently published editorial by Drs. Robert Dluhy and Graham McMahon, editors of the *NEJM*, notes that, *"in the ACCORD trial, there were significant reductions in fatal and nonfatal cardiovascular events in patients who did not have*

known cardiovascular disease before randomization." Dr. John Buse emphasized during the ACCORD press conference that there was no subgroup difference in mortality between the patients with and without cardiovascular disease, but the editorial does suggest that there may be some benefit in low-risk patients that is not seen in high-risk patients.

- **Why was intensive glucose control negative in ACCORD and neutral to positive in ADVANCE?** Some experts have proposed that more weight gain, a faster and more aggressive reduction in A1c, potentially more glycemic variability, more TZD use, more unreported hypoglycemia, or some combination of the above factors in the ACCORD trial may have been involved. Below is a review of important similarities and differences between the two trials:

	ACCORD	**ADVANCE**
Average duration of diabetes	10 years	8 years
Macrovascular disease at baseline	35%	32%
Intensive arm target A1c	6.0%	6.5%
TZD use (Intensive/Standard arms)	92% / 58%	17% / 11%
Duration of study	3.4 years	5 years
Weight gain (Intensive/Standard arms)	3.5 / 0.4 kg	0 / -1.0 kg
Death from any cause (Intensive/Standard arms)	5% / 4%	8.9% / 9.6%
Aspirin use	76%	55%
Statin use	88%	46%

- **The VADT randomized 1,791 US veterans to intensive or standard glucose arms, targeting A1cs of 7% and 8.5%, respectively (the highest goals of any of the three large trials at the meeting).** To be eligible, subjects had to be above the age of 41, with an A1c above 7.5% either on insulin and/or unresponsive to maximal oral agent dose. The study population had a very high mean baseline A1c of 9.4%, with a mean BMI of 31.3. Similar to ADVANCE, the VADT trial failed to show a statistically significant reduction in cardiovascular events in the intensive treatment arm as compared to the standard treatment arm, even though A1c goals were more modest than in ACCORD or ADVANCE; the trial was unique in that it had an especially hard-to-control population (baseline A1c 9.5%). The most interesting finding, in our view, was that severe hypoglycemia over the past three months was the strongest predictor of cardiovascular death (hazard ratio of approximately 3). Microvascular outcomes from the trial will be presented at EASD.
- **Regardless of whether the trials are taken to support or refute the safety of intensive glucose control, none of these results support a push for stricter A1c targets for type 2 patients.** Dr. William Cefalu sums up the implications of these trials very concisely in his *NEJM* editorial, which states that, "with respect to the fundamental question of the effect of glycemic control on macrovascular complications, there should be no misunderstanding that the ADVANCE trial had clearly negative results," while "in the ACCORD trial, the intensive-therapy group had an increased rate of death from any cause." However, he goes on to agree with Drs. Dluhy and McMahon that these trials "should not be interpreted as diminishing the importance of glycemic control." The more specific conclusion to be drawn: "Both trials showed that targeting glycated hemoglobin levels that are below currently accepted standards in high-risk patients with type 2 diabetes did not have a beneficial effect on cardiovascular disease."

- **It is unclear what the results mean for low-risk or average-risk patients without cardiovascular risk factors.** Drs. Dluhy and McMahon comment that, "If hypoglycemia was indeed a contributing cause of death in the ACCORD trial, future studies of cardiovascular risk reduction should focus on targeting near-normal glycemic levels with the use of strategies and therapies associated with a lower risk of hypoglycemia." For now, they recommend keeping current glycemic targets of <7.0% and working to remedy the fact that the established targets for hyperglycemia, hypertension, and hyperlipidemia are only achieved in a few patients (<10% according to NHANES data).
- **Meanwhile, the significant weight gain in ACCORD (presumably from insulin and TZDs and lack of diabetes education) should give a relative boost to the drugs that lower A1c without increasing weight such as metformin, GLP-1 agonists, and DPP-4 inhibitors**. Establishing safety is important, of course, and how safety plays off versus tolerability will also be interesting, particularly in the US environment in which primary care doctors take care of a majority of people with diabetes. We know that the drugs with the best safety records are often difficult to take due to their other side effects (GI side effects, weight gain, etc.). We also know some drugs traditionally viewed as very safe often have records of much higher hypoglycemia, especially severe hypoglycemia, than reported. It will be interesting to see if healthcare economics bodies like NICE (UK) or IQWiG (Germany) will conclude that ADVANCE proves that good control is possible with inexpensive therapies such as sulfonylureas and metformin. Historically such bodies haven't prioritized adherence to therapies as far as we understand, so although patients taking such drugs may get to goal in a randomized, controlled trial, it's not known what will happen in the "real world" outside a controlled study design. We wouldn't necessarily be optimistic.

In our opinion, some of the implications from the three trials are:

1. **More scrutiny of the A1c as a surrogate marker for diabetes control**. The finding that lowering the A1c did not reduce macrovascular complications suggests that it matters not only what the change in A1c is, but potentially also how quickly A1c is lowered and with what agents. The scrutiny of the A1c following these trials may have been a precipitating factor for the recent FDA advisory panel vote in favor of a cardiovascular outcomes trial requirement for all new diabetes drugs (see page 28 for more details).
2. **More of a focus on tight lipid and blood pressure control than tight glucose control** for reducing macrovascular complications. In the words of former ADA President Dr. John Buse, control of blood pressure and lipids for type 2 patients is 'where the money is' in reducing cardiovascular events.
3. **More concerns about hypoglycemia and weight gain**. In the VADT trial, an incident of severe hypoglycemia was strongly associated with subsequent cardiovascular events (hazard ratio of ~3). In ACCORD, the large amount of weight gain (almost 30% had a weight gain of 10 kg in the intensive arm of ACCORD) and asymptomatic hypoglycemia has been implicated in the increased mortality observed in the intensive treatment arm of the study.
4. **More of an interest in earlier interventions**. All three trials had older patients with a relatively long duration of diabetes, and some leading authorities, including Dr. Harold Lebovitz, have proposed that tight glycemic control exacerbates underlying macrovascular conditions in older populations. Many experts have proposed that earlier interventions in patients with a shorter duration of diabetes would have more explicit benefits.
5. **Glimmers of hope that intensive glucose control in the various studies will prove beneficial in the long run.** In some prior studies such as the DCCT, intensifying treatment in

patients with preexisting retinopathy caused a worsening of disease that was reversed in the long run; a similar diverging of outcomes occurred after the eighth year of follow-up in STENO2. The study organizers of ADVANCE indicated that they hope to continue to monitor the vital status of study participants in the future. There will be another follow up after the end of the ACCORD study, expected in 2010. ACCORD is also testing blood pressure and lipids and those results will be available at that time.

6. **Probably no change in the ADA algorithm, or other algorithms.** During a panel discussion that followed the presentation of ACCORD, Dr. Harold Lebovitz, Dr. Robert Rizza, Dr. Robert Sherwin, Dr. Rury Holman, Dr. Sue Kirkman, and Dr. Eberhard Standl were mostly in agreement that the ADA guidelines will not be revised upwards as a result of the study. Dr. Kirkman mentioned that several members of the ADA would be convening very soon with the goal of writing a position paper to be published in a major journal about the implications of ACCORD, ADVANCE, and VADT on clinical practice.

— by Kelly Close, Jenny Jin, and Mark Yarchoan

9. Dialogue with Ms. Rebecca Killion, FDA Patient Representative

Ms. Rebecca Killion is a patient representative on the FDA Endocrinologic and Metabolic Drugs Advisory Committee, a position she has held since 2000. Ms. Killion was diagnosed with type 2 diabetes in 1997 while she was training to the run the Marine Corps Marathon. She then became insulin-requiring after a near-fatal incident of diabetic ketoacidosis in 2001. Ms. Killion was one of two members of the advisory panel to vote against a long-term cardiovascular outcome study requirement for all new diabetes drugs (see page 28 for details). In an interview with Diabetes Close Up, Ms. Killion discusses the rationale behind her vote.

Kelly: Thank you so much for taking our call! We just wanted to have a discussion with you about your role on the panel and your thoughts from a patient's perspective.

Rebecca: That sounds great. I am pleased to have your interest because the more we get diabetes out in front of people, the better it is for everybody.

Kelly: We agree, big-time! And actually, we feel at times the FDA does not pay a great deal of attention to questions related to patient behavior, adherence to medications, or to compliance. How easy is it to take diabetes medication, would you say?

Rebecca: As I said at the meeting, “If it was easy to maintain proper glycemic control, then everyone would have proper glycemic control.” However, it is not easy, and something that was said multiple times at the meeting that really concerned me was, "We have ten classes of drugs.” However, the experience of many diabetics, including myself, is that some of the drugs will work, some of the drugs will not work, some of the drugs will cause intolerable side effects, and some of the drugs are only effective for a short time and then lose their efficacy. You can run through ten classes of drugs pretty quickly.

You have to think about the drugs; you have to give the patient information; and you have to understand what the risks are. Then it is up to the doctor and the patient together to determine what is best. Everybody has to decide about their own care because the burden of care for diabetes rests on the diabetic every day.

Kelly: Since the advisory panel voted to recommend some form of Dr. Nissen’s proposal, would you say you were surprised at how the panel responded?

Rebecca: Usually, every other committee that I have been on, the vote has been a polling of the members going around the table. This time there were buttons on the microphone for yes or no or abstain. After the vote, a chart with all the results came up on the screen. When I saw that the vote was 14 to 2, and I was one of the two no votes, my stomach dropped to the floor! I could not believe that the vote was so lopsided. I could not believe that the majority was agreeing to or promoting something so burdensome.

Kelly: Likewise. Why do you think they did that?

Rebecca: Dr. Nissen is very trendy right now. He has really tapped into a Zeitgeist about fear, litigation, exposure, and risk averseness. He said, "I think that diabetes is glucocentric." Yet, you need to remember that we are not treating heart disease. We are treating diabetes, which is a glucose issue. You need to focus on glucose levels because that is the problem. If you didn't have a problem with your glucose, you wouldn't have a chronic illness. Nissen sees himself as a great advocate for his cardiac patients, and he is, and God bless him for that. But Nissen is a cardiologist, he is not an endocrinologist or a diabetologist, and he does not understand diabetes to the extent of his passion. In terms of diabetic drugs, we are not treating heart disease, we are treating diabetes.

Kelly: I understand where you're headed…

Rebecca: You know, once I had a lay person say to me, "Well, nobody dies from diabetes!" We must to do a better job of educating the public. Diabetes is an illness that can turn on a dime if you are not careful.

Kelly: It is almost like the panel was being asked to trade-off microvascular risk versus macrovascular risk.

Rebecca: In my opinion, that dichotomy was very clearly present, and if you look at the materials that Dr. Ratner presented, his plea was "Do not forget that this is a microvascular illness that also has these macrovascular effects." So you cannot disadvantage one in favor of the other. You have to deal with both effects but not at the expense of each other. This is not a zero-sum game. You don't want to be in a position where you have to trade off some microvascular health to get a little bit less risk on the macrovascular segment.

Kelly: How did you feel about the debate?

Rebecca: It was depressing because I did not think that we were advancing diabetes care by having this kind of debate. I also feel sorry for the FDA because it is between a rock and a hard place at this point. I was thinking back to the AIDS epidemic when the FDA was being lambasted for not bringing drugs to market quickly enough to save lives. Now the FDA is being accused of swinging the pendulum too far the other way and loading up the market with dangerous drugs. The FDA has a difficult task of proceeding with relative caution and still giving people choices in their treatment.

Melissa: From your perspective, how likely do you think the FDA may implement a modified version of Dr. Nissen's proposal, and if they do, how feasible do you feel that the pre-approval and post-approval trial looking at cardiovascular risk will be?

Rebecca: It is hard for me to predict what the FDA will do. I think it is very likely that they will adopt some kind of modified proposal. It will not be Nissen's approach entirely, but I think it would be unlikely for the FDA to not institute some kind of pre- and/or post-approval trials. I believe we will come to some compromise on it because if they try to enact Nissen's proposal without some more reasonable approaches, it will be detrimental for diabetic patients.

How it plays out and how feasible it is, I think we'll find out. It will be something that evolves over time, and I believe it will end up being a question that is reevaluated. As I said, my two concerns are that this decision is going to have a chilling effect on drug development and that it also will delay new drugs coming to market.

Kelly: What do you think is the best case scenario and what is the worst case scenario?

Rebecca: I would say the worst case scenario is that we have fewer drugs that are even being considered because of these burdens. You are going to have fewer drugs that are going to be developed; you are going to have less innovation; and you are going to have a chilling effect on the development of diabetes drugs. That is the last thing that needs to happen when you have a disease that is reaching epidemic proportions, worldwide.

Best case scenario would be some modification of the trials that results in an improved ability to discern risks, and not just risks with respect to diabetes. If you can find a way to refine the trials so they are better able to discern these unexpected risks, then I think that would be the best case scenario.

Kelly: When do you think the FDA will come back on this issue?

Rebecca: The timing of decisions by the FDA is variable. They can come out very quickly, or they can be taken under advisement for quite a long time. It depends on a lot of different factors. I don't think that they're going to be coming out very quickly with a decision on this because, whatever course they choose, it is going to have to be very thoroughly considered.

Kelly: One thing that surprised us was the absence of ADA. Were you surprised that ADA was not present?

Rebecca: I was actually very surprised because that has been contrary to my experience. Almost every other panel I've been on there have been multiple speakers, and this meeting only had three. The meeting description was very vague, and the purpose for the meeting was kind of nebulous. I reviewed all the background materials, and I have to say that when I arrived I still wasn't sure what the meeting was about.

Kelly: I think it's too bad that we didn't think to publicize it more. Next time we will, especially to patients. One final question, you mentioned that you took Symlin. I don't know if you knew, but Symlin was actually rejected by the FDA for type 2 use unless the person was on mealtime insulin.

Rebecca: No, I didn't know that. When I started taking Symlin, I was able to reduce my insulin requirement by 50%, and I lost 27 pounds. It has been a great drug for me. This is where I think the patient community is so vital. You cannot abdicate your responsibility as a patient and, one would think, with the number of diabetics in this country, that they could be a very forceful voice. Diabetics should be encouraged to contact the FDA about their experiences with medications, both good and bad, so that FDA can make more informed and realistic decisions. The FDA includes patient representatives, like me, to obtain a patient perspective when considering drug approval. This perspective is too important to confine to advisory committee meetings only. Diabetics need to be advocates too and should not hesitate to contact the FDA, Congress, pharmaceutical companies, and other decision-makers to highlight the issues that matter to diabetics everywhere.

Kelly: This is so valuable to hear. Rebecca, thank you again for your time. We really enjoyed gaining your perspective on the FDA advisory meeting, and we salute you for all you do in the name of diabetes and patients.

— by Kelly Close and Melissa Tjota

10. Interview with Dr. Harold Lebovitz – ADA '08 Download

Dr. Lebovitz is Professor of Medicine in the Division of Endocrinology and Metabolism at the State University of New York (SUNY) Health Science Center at Brooklyn. He has served on numerous review committees for the American Diabetes Association, the National Institutes of Health, and the Veterans Administration, and has served on the editorial boards of Diabetes, Obesity and Metabolism, Diabetes Care and the Journal of Clinical Endocrinology and Metabolism. His main clinical research interests are in the Pathogenesis of type 2 diabetes, pharmacologic and interventional strategies to treat type 2 diabetes, racial and ethnic differences in type 2 diabetes, and the effects of body composition on metabolic processes. In an interview with DCU, Dr. Harold Lebovitz shares his thoughts about the ADA 68th Scientific Sessions and discusses his role as Program Chair at this year's meeting.

Kelly Close: Dr. Lebovitz, brilliant ADA! It was absolutely fantastic, and we've heard such great feedback about it from so many people with whom we speak on a regular basis. Congratulations!

Dr. Lebovitz: Thank you. It was a fabulous effort from a lot of people and in particular the entire scientific program committee.

Dr. Lebovitz comments on the recent presentations at ADA

Mark Yarchoan: To start off, one of the sessions we were curious to see the late breaker where Symlin was used on top of basal insulin as a replacement for rapid acting insulin. Since Symlin is not FDA-approved for that indication, and since we hear from readers of *diaTribe* (our patient newsletter) wondering about this, we were curious if you thought that was a political decision by the ADA to include it. It's also on our mind since we just spoke to FDA patient representative Rebecca Killion who takes Symlin … (ed. note – see page 40).

Dr. Lebovitz: No, it was not a political decision because when you are on a program committee, you are interested in having new and exciting information presented. The information that is presented has nothing to do with whether it is approved by the FDA or not. If we waited for everything to be FDA approved before being presented, we would have to eliminate most of the exciting things that are currently happening.

The first study that had been presented looked at adding pramlintide to glargine (Lantus), but it was compared against a placebo. So that was really interesting; it was a piece of science saying that if you added pramlintide, this is what you would get. The next question then would be how does it compare with other things that you might use like mealtime insulin. We were actually surprised when we read the abstract.

Kelly: Interesting. How do you mean?

Dr. Lebovitz: I would have originally thought that prandial insulin would have a better effect.

Mark: Gotcha. Do you think the presentation of that data could influence the FDA in the future? We hear a lot from patients that they would like more alternatives, given that every drug doesn't work for every patient either due to efficacy or tolerability issues.

Dr. Lebovitz: That was never really a consideration. The scientific session really is absolutely unbiased in terms of commercialization. We almost never allow anybody who is associated with a company to present even though there are many good people who work for companies.

Kelly: Some people have said that they learned less this year about devices. Can you talk about how the number of device abstracts vary from year to year?

Dr. Lebovitz: Again, that depends a little on the program committee. We had so many device presentations the year before, so in terms of balancing the program, we looked at what was really new in the device area compared to what had been presented last year.

Kelly: On incretins, Novo Nordisk had a press release on liraglutide just before the meeting – there was some controversy over this since it was not presented at the meeting and we wondered if you had any thoughts on this.

Dr. Lebovitz: To be perfectly honest, I did not like it. You have to remember that these are press releases and they have limited credibility because you cannot see the actual data. There were many very good liraglutide abstracts submitted and presented at the Annual Meeting. I would have preferred that they either submitted that material discussed in the press release as a late breaking abstract or held the press release until after the Annual Meeting

Kelly: Going back to drugs, we were wondering what you thought about new data at this meeting – let's start with SGLT-2 inhibitors.

Dr. Lebovitz: I thought the data were very good. We had a presentation in a symposia and then we had a number of presented abstracts showing data on SGLT-2 inhibitors . There were effects that you might have anticipated with SGLT-2 inhibition that could have been a problem; however, the data showed that they were not, and that was very positive for them as potential therapeutic agents to treat diabetes. For example, you might have thought that people would get dehydrated or have electrolyte imbalances. Apparently that was not the case according to the data from the Phase 2 studies that were presented. You might expect that there would be an increase in urinary tract infection, and there was a small but hardly dramatic increase. Overall, I think the Phase 2 data looks very promising, which means that we need to look very carefully at the Phase 3 data to see how good these agents are. From the data presented, it suggests that this may be a viable new class of drugs.

Kelly: What about other new data on the drug front? What did you think of exenatide once weekly data – that seemed to be the most highly awaited.

Dr. Lebovitz: Several oral presentations discussed the results of the phase three trial comparing the treatment of type 2 patients with once weekly exenatide-LAR and the currently available exenatide twice a day. Exenatide-LAR was superior in terms of decrease in fasting plasma glucose, decrease in HbA1C and weight loss. The effects of exenatide-LAR were sustained for 52 weeks, which was the length of the follow-up.

Mark: There appeared to be some negativity emerging at this meeting about the sulfonylurea class and insulin in light of the severe hypoglycemia concerns coming out of the VADT. What did you think about that?

Dr. Lebovitz: First of all, with sulfonylureas, I do not believe there was anything more negative than has been in the past. Sulfonylureas always present the problem of weight gain and hypoglycemia, but I also think that there is a lot of new, exciting information from the past few years to show that there are specific types of diabetes in which sulfonylureas are the ideal treatment, particularly neo-natal diabetes and some forms of MODY involving abnormalities in the K^+-ATP channel. If you have difficulty with the K^+-ATP channel, either it cannot recognize the ATP or there is some problem with its mechanism of closure, sulfonylureas bypass glucose and actually close the channel. So, I think there are two things that you can say about sulfonylureas that have emerged. One is that there are some classes of diabetes in which they are really the treatment of choice—above and beyond that of insulin or anything else. In fact, people with neo-natal diabetes were for many years thought to be a variant of type 1 diabetes, and they have always been treated with insulin.

This was never ideal and certainly had no benefit on those with neurologic abnormalities. Since they have been treated with sulfonylureas, they have been really well controlled, and some of them have had improvement in their neurologic problems.

Dr. Lebovitz comments on the lack of attention given to diabetes

Kelly: At ADA, there was much more this year about individualization of therapy. On the one hand, it flies in the face of our health care system where upwards of 60-70% of people see a primary care doctor who does not get reimbursed to see people for a very long time. On the other hand, from a patient perspective we can certainly see that it is optimal, even necessary.

Dr. Lebovitz: That is a big problem because diabetes has not gotten the same degree of priority in the health care system as cancer and heart disease. As we learn more about the different pathogenic bases of diabetes, specific therapies based on the underlying pathophysiologic abnormalities and individual pharmacogenetics will become widely accepted. Physicians and other health care providers will need to spend more time to understand and treat the individual diabetic patient.

Kelly: That is troubling because we are in a system where patients receive only a few minutes of care – on average – if they see a PCP. I know you have commented before how different this is from other countries. Can you say a bit more about how diabetes drug assessment differs from other areas?

Dr. Lebovitz: For each cancer you have a specific group of chemotherapeutic agents and monoclonal antibodies that have been developed. The government will pay huge premiums for an Avastin or Gleevec. There is no recognition that diabetes is different and that there may be people with diabetes who need a specific drug. As we discover more about different kinds of diabetes, we can say, "There are some drugs that are indicated for one group of people and other drugs for another group." Not everybody responds to every drug in the same way. For example, if you take sulfonylureas, we know that for brand-new patients with type 2 diabetes about 60-70% will get a good or a very good response to sulfonylureas; however, there are approximately 25% who are primary failures. That must mean that there is a different defect. Another example are the incretins where some 10-20% of patients given Exenatide do not have a significant response.

Kelly: Why does that happen?

Dr. Lebovitz: It means that they either have a different defect or that they handle the drug differently. In other words, one of the primary focuses in pharmacogenetics is how somebody handles a drug. They may have a slightly different receptor, or they may metabolize the drug differently. All of these things can change, and these are the areas that we are just beginning to get insights into.

Kelly: Do you believe we could use some of this information to improve the amount of attention that people with diabetes get?

Mark: As a follow-up to Kelly's question, do you believe that we will get to the point where someone can take a fairly simple test that will tell them what the basic abnormality is? For example, a test could tell someone with type 2 diabetes if they have insulin resistance or hepatic glucose or incretin access; thus, the therapy can be targeted?

Dr. Lebovitz: I don't think that is going to work. I think what will work is when we find the specific pathophysiologic abnormality. In other words, if we find out why the particular mechanism is not working. Then you can begin to target treatments differently. Let us make a

presumption that there is an enzyme that can break down Exenatide or Liraglutide—different than DPP4 inhibitors —and let us say that the enzyme is only present in significant amounts in 15-20% of the population. That might be the 15% of patients that these drugs do not work in. What we are dealing with is how the body deals with a particular agent.

Kelly: Should we be concerned because there are so many patients out there who do not fit the profile of an average patient? Individualization of therapy is hard to do in a PCP office, no?

Dr. Lebovitz: Well, that is the way our system is set up because it provides an algorithm for the average patient. If you're not an average patient, you would hope that the patient would be referred to a specialist.

Kelly: How much of the time do you think that happens?

Dr. Lebovitz: I suspect it does not happen as often as it should. That is why you need a health care system in which there is a close relationship between the primary care physician and the specialist. That is what they do in England where they have Shared Care. We do not do this in the US, and that is a deficiency in our health care system.

Kelly: Could you tell us a little bit more about your thoughts on insulin data at the meeting and related side effects and what all that means for patients and providers?

Dr. Lebovitz: My personal opinion about insulin treatment is that you are going to see much more concern about weight gain. In the past, we have not really paid as much attention to the importance of weight gain during therapy in people with type 2 diabetes. VADT and ACCORD both demonstrated that if you really pushed insulin treatment in type 2 diabetic patients, you will get a huge amount of weigh gain and significant severe hypoglycemia. One needs to rethink how aggressive insulin therapy in patients with type 2 diabetes should be.

There was a presentation given by Kathleen Flegal from the CDC, in which she presented population-based mortality data. The lowest mortality is in overweight people. People who are mildly overweight live longer. People who are underweight actually have a shorter lifespan, which is usually due to infections. In the overweight group, even though there was a lower mortality, there was an increased mortality from diabetes but a decreased mortality from other things. In obese people, there is an increased mortality from cardiovascular disease, from diabetes, and from cancer. There is additional data that raises the question about whether obesity itself in patients with diabetes contributes to some bad outcomes. The net result will be more focus on finding treatments that are either weight neutral or lead to weight loss. One of the things about the SGLT-2 inhibitors is if you lose calories from glycosuria, then you should get some weight loss. These could be another class like the incretin mimetics that will cause weight loss. In the future, you may see more interest in looking for ways of treating diabetes with weight loss which is why some of the surgeons are beginning to promote their bariatric surgical procedures.

Dr. Lebovitz comments on ADVANCE, ACCORD, and VADT

Kelly: Could you say a little bit more about ACCORD? What your expectations were and what you thought of the panel?

Dr. Lebovitz: I believe that you have to take the three studies together – ACCORD, ADVANCE, and VADT. My conclusion from the three studies is that lowering A1c does not cause an increase in death. It is the strategy that was used in ACCORD that led to the increased mortality. What component of the strategy was deleterious is unknown. It could have been the hypoglycemia or the tremendous weight gain or some other factor. I don't know that they

are ever going to dissect that and find out what the cause was. What you can say is that the strategy really caused an increase in mortality.

Kelly: Could we look at those who died and look at their A1c and weight?

Dr. Lebovitz: My first point is that they are doing all of that, but they are unable to come up with any real answer at the moment. My second point is that the three studies show that if you take people who have had longstanding diabetes, significant cardiovascular disease, or very high cardiovascular risk, the intensive glycemic control really does not cause any decrease in macrovascular disease. However, it does not say anything about intensive glycemic control in people at the earlier stages of diabetes. The VADT data from their secondary analysis and their calcium coronary studies suggests that if you did have intensive glycemic control in people at the early stages of diabetes, you might actually see a decrease in cardiovascular events from intensive glycemic control. However, that data is not definitive and is only worthy of hypothesis testing.

Kelly: So do you think the way that ACCORD was designed was so the trial did not have to be as long as to see cardiovascular deaths?

Dr. Lebovitz: Absolutely. In other words, all of these studies are done with people who have significant disease or significant risk factors because the event rate should be high enough that you do not need a long duration study. In other words, five years is good—10,000 people for five years rather than 30,000 people for 15 years. The trouble is if you do an intervention study very early, the event rates are low for many years making it an untenable study to do.

Kelly: In hindsight, was it smart to look only at people in such a select group – Dr. Buse said that the people who would "resemble" the ACCORD participant group would be about 10-20% of all type 2 diabetic patients.

Dr. Lebovitz: Clinical trials attempting to show decreases in clinical cardiovascular events are becoming very difficult to do. Appropriate medical care requires patients to be on statins, ACE inhibitors or ARBs, aspirin and additional agents to control other significant CV risk factors As a result CV event rates are decreasing. The most significant cardiovascular risk factors are age and a previous cardiovascular event. If you take people with longer duration diabetes who have had a previous CV event, then the event rate will be the highest. That is why the populations selected have had long standing diabetes and previous clinical CV events . Even at that, the event rate in ACCORD was much lower than what they had predicted.

Kelly: What about microvascular risk? Where does that all fit in?

Dr. Lebovitz: The only study that looked at that was ADVANCE, and they found a 20% decrease in kidney problems. The other two studies have not presented microvascular disease data yet. I would predict that they will show that better glycemic control reduces microvascular events.

Kelly: There seems to be a lack of emphasis on the importance of this, disappointingly. I also understand that UKPDS is going to report again in a couple of years. Would you speculate that it may show reduced microvascular risk?

Dr. Lebovitz: I don't know. You have to understand though that UKPDS was not an intensive control study. What they did was take a group of people and start them on individual therapies. They did not change the therapy until the fasting glucose got to be 270 mg/dL. You have to go back and look at the design. It was not a tightly controlled study.

Kelly: About another study, can you comment on the 4T trial and glycemic variability? Were you expecting to see more differences between the intensive insulin arm versus the baseline?

Dr. Lebovitz: Well, I saw the one-year data, but I haven't seen the two-year data yet. It was an intensive insulin treatment study in which patients failing oral agents had a basal, a prandial, or a mixed insulin twice a day, added to their treatment regimen. They got down to hemoglobin A1cs of 7.2, 7.3, and 7.6, but at the expense of a great deal of hypoglycemia and significant weight gain. It will be interesting to see what the second year shows. You also have the three studies comparing the addition of exenatide to the addition of basal or mixed insulin twice a day in type 2 diabetic patients failing oral agents which showed that the addition of exenatide reduces HbA1c as well as the addition of insulin with the advantage of weight loss rather than weight gain. It certainly suggests that there are significant alternatives to thinking about adding insulin, at least at that stage.

Kelly: I guess it is about what path you take to get to a low A1C or to any A1C.

Kelly: The other question we had about insulin and insulin delivery was that at some point there is beta cell burnout in type 2 patients. There are 8 million people out there that could possibly have beta cell burnout – or at least they are not at a glycemic goal of 7 or lower A1c. Do they need an easier way of taking insulin? Do they need faster insulin?

Dr. Lebovitz: I don't know because we have not done a good job with insulin treatment in those people. There is no good study that shows insulin treatment in those people has any benefit. You can talk about A1cs, but when you talk about clinical outcomes, there are no data. It'll be very interesting to see the results from the Origin study. Hopefully, that data will come out someday soon.

Kelly: Could you talk about takeaways from the meeting for pre-diabetes? The awareness seemed to be significantly higher this year.

Dr. Lebovitz: We recognize that pre-diabetes is a very important entity and that delaying or preventing its progression to diabetes is likely to be beneficial. Many questions remain to be answered such as when lifestyle fails what pharmacologic agents if any are indicated; how do we monitor such patients; how should we identify patients with pre-diabetes; will treating pre-diabetes reduce macrovascular complications.

Kelly: As our final question, could you tell us a little bit more about the video that ADA put together?

Dr. Lebovitz: ADA put together a one-hour tape with highlights of the meeting in which they interviewed about 15 investigators during the meeting. We had a meeting in Chicago on June 18th where we edited the video presentations, and after each group of presentations we had a panel discussion to review and clarify the significance of what was presented. It's the first year they've done it, and I'm told they got a very nice response from it. It's available for viewing on the ADA website.

Kelly: Wonderful! Thank you so much for you time. This conversation has definitely been above and beyond the call. We so appreciate all you have done for the field in your research, your patient interactions, and your planning for these meetings.

— *by Kelly Close, Melissa Tjota, and Mark Yarchoan*

11. Literature Review: Intensive Glycemic Control and Cardiovascular Disease Observations from the ACCORD Study

Cefalu, W.T. and Watson, K. Diabetes, July 2008.

In the July issue of Diabetes, Drs. William Cefalu and Karol Watson discuss the value of intensive glycemic control in type 2 diabetes in light of the recent interim report from the Action to Control Cardiovascular Risk in Diabetes (ACCORD) trial. The intensive treatment arm of the ACCORD trial was halted early due to an apparent increase in mortality associated with intensive therapy. The ACCORD trial enrolled patients with baseline cardiovascular disease or at least two cardiovascular disease risk factors in addition to type 2 diabetes. As a result, patients in ACCORD were at substantially higher cardiovascular disease risk than the average patient with type 2 diabetes. Consequently, the findings of ACCORD may not apply to all patients with type 2 diabetes. Findings from similar studies have not found increased mortality associated with intensive glycemic control, and substantial evidence indicates that intensive glycemic control reduces the risk of microvascular diabetes complications. Taken together, this information indicates that the current ADA guidelines for glycemic control in diabetes (A1c < 7.0%) should be followed. Intensive glycemic control may not be optimal therapy in patients with diabetes and high cardiovascular disease risk. Regardless of the ultimate conclusion based on the final analysis of ACCORD and similar studies, evidence strongly supports the use of intensive therapy for cardiovascular disease risk factors such as high blood pressure and dyslipidemia as a standard part of type 2 diabetes care.

- **The recent decision to halt the intensive glycemic control arm of the Action to Control Cardiovascular Risk in Diabetes (ACCORD) trial due to an apparent increase in mortality came as a significant surprise to the diabetes treatment community.** Prior to this study, doctors and other diabetes specialists had widely assumed that intensive glycemic control would decrease mortality, and that this decreased would be most apparent in patients with high baseline cardiovascular disease risk.

- **Intensive glycemic control clearly decreases the risk of microvascular complications from diabetes.** Intensive glucose lowering therapy decreases the risk of nephropathy, neuropathy, and retinopathy in patients with diabetes.

- **Currently, we lack definitive evidence that intensive glycemic control can improve cardiovascular disease risk or all cause mortality in patients with diabetes; however, we have substantial evidence suggesting a protective effect of intensive diabetes therapy.** Several studies have shown a correlation between increased A1c and cardiovascular disease risk, and A1c levels appear to account for most of the excess mortality in men with diabetes. Intensive glucose lowering therapies have been shown to improve cardiovascular disease outcomes in some populations after substantial periods of follow-up.

- **The ACCORD study enrolled approximately 10,000 patients with type 2 diabetes and high baseline cardiovascular disease risk.** Patients were randomly assigned to either an intensive treatment arm with a goal of achieving an A1c below 6.0%, or a standard treatment arm where the A1c goal was 7.0% to 7.9%. Any clinically approved diabetes therapy could be used to achieve these goals. In addition, patients were randomly assigned to intensive or standard therapy for high blood pressure and dyslipidemia.

- **The median A1c in the intensive glycemic control arm of ACCORD was 6.4% compared to 7.5% in the standard treatment arm.** 257 patients died in the intensive treatment arm compared to 203 in the standard treatment arm. Deaths were not associated with

the use of any specific medication; however, given the size of the study and the range of drugs used, establishing a statistically significant connection to a particular medication may not be possible. In addition, hypoglycemia did not appear to be sufficient to account for the increased mortality.

- **The patients enrolled in ACCORD may not reflect the majority of patients with type 2 diabetes.** ACCORD was the first trial to prospectively assess the value of achieving an A1c below 7.0%, the current treatment guideline set by the ADA. All of the patients in ACCORD either had pre-existing cardiovascular disease or at least two cardiovascular disease risk factors in addition to diabetes; as a result, the findings may not be readily applicable to patients with diabetes who do not have similarly high cardiovascular disease risk

- **Treatment of high cholesterol and high blood pressure substantially reduces cardiovascular disease risk in patients with diabetes.** The Steno-2 trial found a significant decrease in cardiovascular mortality associated with combination therapy for high blood pressure, dyslipidemia, and hyperglycemia. The ACCORD trial should provide additional evidence supporting the use of intensive therapy directed at cardiovascular disease risk factors in patients with type 2 diabetes.

- **Several other studies are examining treatment strategies that are similar to those used in ACCORD.** These studies include the Action in Diabetes and Vascular Disease: Preterax and Diamicron-MR Controlled Evaluation (ADVANCE) trial, as well as the Veterans Affairs Diabetes Trial (VADT). Both of these studies will examine the risk of cardiovascular disease in patients with diabetes who are treated with intensive therapy aiming to lower A1c to < 6.5%.

- **To date, ADVANCE has not shown a negative association between intensive glycemic control and cardiovascular disease risk.** The reason for the difference between ADVANCE and ACCORD is not yet clear, though it may relate to the actual A1c levels achieved, the specific mediations used (ADVANCE relies heavily on sulfonylureas), or the baseline cardiovascular risk rates in the enrolled populations.

- **The wording in the current ADA guidelines is appropriate even in light of the preliminary findings from the ACCORD trial.** Current ADA guidelines suggest an A1c below 7.0%, acknowledging an increased risk of hypoglycemia associated with intensive glycemic control. ADA recommendations also include individualized treatment goals, particularly for children, pregnant women, and elderly patients.

- **Less intensive regimens for maintaining glycemic control may be warranted in patients with type 2 diabetes and high cardiovascular disease risk.** Further studies will be necessary in order to address whether patients with shorter duration disease or lower cardiovascular disease risk will benefit from intensive glycemic control. In the meantime, aggressive therapy to manage other cardiovascular disease risk factors is indicated in high-risk populations.

— by Michael Dougan

12. Conference Preview: AADE Annual Meeting

August 6- 9 • Washington, DC • www.diabeteseducator.org/ProfessionalResources/AnnualMeeting

From August 6-9, the American Association of Diabetes Educators (AADE) will hold its annual meeting in Washington, DC. This year's meeting appears to have lots on continuous glucose monitoring (CGM) and a number of talks will focus on conveying the impact of sleep, food, exercise, medication, and

depression with the goal of encouraging patient empowerment and helping develop strategies that improve self-care behavior as well as daily diabetes care. There seems to be an ongoing focus at the meeting on earlier interventions in diabetes and pre-diabetes, and lifestyle interventions for the prevention of diabetes and pre-diabetes. Below is a list of some of the key talks – there were far too many to mention all so go through your planner carefully!:

Tuesday (August 5)

- **Medications, Monitoring and Diabetes Management: Using Continuous Glucose Monitoring (CGM) Technology to Guide Therapy Changes.** Jennifer M. Block, RN, CDE (Stanford University, Palo Alto, CA) and Margaret Powers, PhD, RD, CDE (International Diabetes Center, Minneapolis, MN). This pre-conference program focuses on discussing current and future research on CGM use – we're very excited to get the take from two educators who have both used CGM extensively.

- **Demystifying Hyperglycemia: Management Throughout Hospitalization In-Patient Care – Along the Continuum: Case Studies for the Advanced Practice Diabetes Educator.** Jane Seley, MPh, MSN, CDE; Shannon Bailey, MD, RD/LD, CDE; Carol Manchester, MSN, APRN, BC-ADM, CDE; and David Baldwin, MD.

Wednesday, August 6

- **Political Commentary**. Chris Matthews, Political Commentator and Chevy Chase, MD. Since Chris Matthews was hospitalized last year with complications from diabetes, it will be interesting to hear his take on diabetes education and maintaining a healthy lifestyle.

- **While You Were Sleeping: Implementing a Sleep Apnea Screening Protocol.** Virginia Zamudio-Lange, RN, MSN, CDE.

- **Glucose Monitoring – Does it Make a Difference?** Virginia Valentine, CNS, BC-ADM, CDE CEO; Guillermo Umpierrez, FACP, FACE; and Andrew J. Drexler. This will be a point-counterpoint debate about the utility of BGM.

- **Diabetes Drug Therapy in a Changing Market.** Evan M. Sisson, PharmD, MHA, CDE (VCU School of Pharmacy, Richmond, VA). This session will identify the increased challenges that diabetes educators and providers face as they synthesize new drug therapy evidence – we think this is a major challenge because the side effect profiles of many drugs can prompt low adherence to medication, which in turn prompts failure to reach glycemic targets, which in turn prompts greater long-term complications. We will be interested to hear their take on a variety of subjects, especially the "ADA algorithm" for treating diabetes.

- **Anti-Diabetic Medications in the Pediatric Diabetes Population.** Renee M. Meehan, MA, BSN, RN, CDE (Tampa General Hospital, Tampa, FL). This talk will discuss an overview of what drugs are available and FDA approved for treatment of type 2 diabetes in children. We know metformin and insulin are approved for pediatric use – we are interested to hear the speaker's take on other drugs in the armamentarium.

- **The ACCORD Study**. Kevin Peterson, MD, MPH (University of Minnesota, Minneapolis, MN). Dr. Peterson will review the ACCORD study and will discuss implications for clinical practice. type 2 diabetes. We will be interested in hearing Dr. Peterson's conclusions and opinions on ACCORD's trial design and execution.

Thursday (August 7)

- **Strategies for Primary and Secondary Prevention of Type 1 Diabetes. Jay Skyler, MD, MACP (University of Miami, Miami, FL).** Dr. Skyler will discuss recent type 1 diabetes prevention studies – we are particularly interested to hear his thinking on anti-CD3, the progress made in the trials thus far, dropout rates, reported serious adverse effects, possible long term health consequences and what Dr. Skyler sees as the most important risks to consider when weighing the risk benefit ratio for trial participation.

- **Understanding and Managing Hypoglycemia. Katie Winger, EdD, RN (Joslin Diabetes Center, Boston, MA).** This symposium by top educator Katie Winger will describe the physiology underlying the symptoms and cognitive changes associated with hypoglycemia, its impact on relationships and patient safety, and clinical strategies that are useful for preventing severe hypoglycemia.

- **Optimizing the Value of Self-Monitoring of Blood Glucose**. Barry H. Ginsberg, MD (Diabetes Technology Consultants, Wyckoff, NJ). This presentation will cover the sources of the errors in self-monitoring of blood glucose – Dr. Barry Ginsberg is a real guru on patient behavior and we enthusiastically look forward to his talk.

- **Providing Diabetes Intervention Services in an Automobile Assembly Plant.** Roger P. Austin, MS, RPh, CDE. Managing diabetes takes a great deal of time and effort, and many people do not have to time to attend sessions where they can learn how to better manage their disease. We look forward to hearing how rather than getting the patient to a diabetes education program, the diabetes educator brings it to the patients.

- **How to Actually MAKE Money Providing Diabetes Education.** Gary Scheiner, MS, CDE. Gary is an incredibly valuable resource to patients and providers – this should be a popular session and we hope it is well – publicized since in our view, educators are about the most underpaid medical specialists that we know of, along with pediatricians. Endocrinologists are not far behind.

- **Home Continuous Glucose Monitoring: A New Perspective on Pathophysiology and Treatment.** Howard A. Wolpert, MD; Stacey O'Donnell, RN, BS, CDE; and Diana Stuber, MA, RD, CDE. This trio will undoubtedly give a blizzard of valuable information on CGM – this will likely be a very packed session.

- **Multidisciplinary Strategies in T2DM: A Critical Update on Performance Improvement and Excellence in Care.** Edward Horton, MD (Moderator); Mary Ann Banerji, MD, FACP; Susan Cornell, BS, PharmD, CDE, BC-ADM; and Davida F. Kruger, MSN, APRN, BC-ADM. Another powerhouse team… this is not to be missed.

- **The JDRF Artificial Pancreas Project - CGM and Beyond**. Aaron Kowalski, PhD (Juvenile Diabetes Research Foundation) and Laurel Messer RN, BSN, CDE (University of Colorado Health Sciences Center, Aurora, CO). Dr. Kowalski and Ms. Messer will provide an up-to the minute view of the rapidly evolving world of diabetes technology. All eyes will be on Aaron if the data isn't out yet for the JDRF trial on CGM – and probably even if it is.

Friday (August 8)

- **Prevention of Type 2 Diabetes: Is it Time?** Robert E. Ratner, MD (MedStar Research Institute, Hyattsville, MD). Dr. Ratner will discuss why more preventative measures need to be

taken to treat pre-diabetes – we're very excited to hear this as Dr. Ratner is among the most respected clinicians in diabetes practice today.

- **New Therapeutic Horizons: Mapping the Future of Glycemic Control with Incretin-based Therapy.** R. Keith Campbell, RPh, MBA, FASHP, CDE (Washington State University College of Pharmacy, Pullman, WA); Betty P. Brackenridge, MS, RD, CDE (Diabetes Management & Training Centers, Phoenix, AZ); and Donna M. Rice, MBA, RN, BSN, CDE (Botsford General Hospital, Brighton, MI). This powerhouse team will discuss incretins and the real skinny (so to speak) – we'll be very interested to hear their collective view on how incretins compare to the rest of the diabetes armamentarium.
- **The Family Approach: Improving Adolescent Adherence to Medical Regimen.** Joseph Solowiejczyk, MS, RN, CDE. He's an amazing speaker and has been in the trenches – don't miss this one.
- **Clinical Discourse: Peer Exchange and Interactive Audience Generation.** Davida Kruger, MSN, APRN-DC, DC-ADM; Richard W. Nesto, MD; and John B. Buse, MD, FACE. The faculty at this year's AADE is incredible – this is yet another session not to even consider missing.
- **Clinical Discourse: Utilizing Incretin Therapies to Minimize Dysmetabolic Risk Factors in Diabetes Management (Amylin/Lilly).** Catherine L. Martin, MS, APRN, BC-ADM, CDE (University of Michigan, Ann Arbor, MI); Joseph A. Aloi, MD (University of Virginia, Charlottesville, VA); and Frank Svec, MD, PhD (Louisiana State University Health Sciences Center, New Orleans, LA).

Saturday (August 9)

- **Translating Science into Practice: Research-based Tools from the NIH. Judith Fradkin, MD, BS (NIDDK, Bethesda, MD)** Dr. Fradkin will discuss ongoing NIH clinical trials, recent clinical research results, and research on how best to translate research findings into clinical practice. Presumably, Dr. Fradkin will discuss the implications of the recent ACCORD trial – we are looking forward to her take. We interviewed Dr. Fradkin in DCU #80 (May, 2008) and found her to be phenomenally interesting.
- **Solutions to the Diabetes Epidemic. Ann Albright, PhD, RD (CDC, Division of Diabetes Translation, Atlanta, GA)** Dr. Albright (we call her Dr. Albright The Great) will speak about what solutions are needed that focus on primary and secondary/tertiary prevention, address populations hardest hit by diabetes, and that have evidence of effectiveness. She is devoted to public health and the field is lucky to have her leadership at CDC.
- **Diabetes: The Global Epidemic and Children Around the World, Francine Kaufman, MD, Children's Hospital.** As always we can't wait to hear Dr. Kaufman, one of the most inspired and inspiring speakers of our time. If you haven't read her book Diabesity, please pick it up pronto to gain a very deep understanding of the dire public health issues facing our planet.

—by Kelly Close, Melissa Tjota, and Mark Yarchoan

13. Diabetes Comings and Goings

- **Claudia Graham** has left Medtronic and her role there as Vice President, Global Therapy Access. She will continue her work on reimbursement as a private consultant. We suspect she will be inundated with requests and we certainly hope she will be from a patient perspective.

- **Alec Winton** has been appointed General Manager, UK of WaveSense, Inc. He previously worked at Menarini Diagnostics.
- **William A. Hawkins**, Chief Executive Officer of Medtronic, will replace Arthur D. Collins Jr. as Chairman of the Board of Directors.
- **Elie Farah** has assumed the position of President of Transition Therapeutics; he also continues to serve as the company's Chief Financial Officer.
- **Nicole Rusaw-George** has been appointed to the position of Vice President, Finance of Transition Therapeutics. She was previously a director of finance at the company.
- **Martin P. Bedigian, MD,** has joined Isis Pharmaceuticals as Vice President and Chief Medical Officer.

14. DCU Stock Chart and Final Thoughts

	17-Jul-08	17-Jun-08		2-Jan-08		17-Jul-07		IPO		Market Cap
GSK	46.97	42.12	12%	50.17	-6%	53.12	-12%	-	-	$ 125.5 B
NVO	63.12	62.51	1%	63.8	-1%	54.73	15%	-	-	$ 44.7 B
AMLN	26.32	26.20	0%	36.95	-29%	42.96	-39%	14	88%	$ 3.5 B
PODD	16.55	16.52	0%	23.42	-29%	13.99	18%	15	10%	$ 440 M
BIOD	16.20	15.15	7%	22.65	-28%	18.50	-12%	15	8%	$ 376 M
OREX	8.50	8.32	2%	13.94	-39%	15.71	-46%	12	-29%	$289 M
MNKD	2.80	2.77	1%	7.86	-64%	12.75	-78%	14	-80%	$279 M
DXCM	7.21	7.65	-6%	8.95	-19%	9.51	-24%	12	-40%	$206 M
HDIX	7.90	8.04	-2%	8.45	-7%	11.50	-31%	12	-34%	$ 142 M

There hasn't been a lot of movement over the last month in diabetes – biggest movers are Biodel, unsurprising in light of new data out. GSK has moved up quite a lot although we don't think diabetes goings-on are responsible for this. All in all, a sleepy month in terms of stock movement and we look forward to seeing what happens next month!