DIABETESCLOSEUP

The Leading Source of Diabetes Business News

ADA is in the Air **May 2008 • No. 80**

From the Editor

Do you hear that rumble? It's the sound of 13,000 researchers, healthcare providers, industry representatives, and our full Close Concerns team preparing to descend upon the Moscone Center in San Francisco to attend the American Diabetes Association (ADA) Annual Scientific Sessions that starts next Friday, June 6.

Indeed, ADA is in the air. Every year when the ADA abstracts come out, I feel like it's Christmas. It's possibly my favorite day apart from family birthdays and anniversaries. Heck, it nearly beats St. Patrick's Day, so you know I'm being serious! In previous years, I've written that various people (like John Close) have suggested that I not admit in public my love of ADA abstracts – a clear sign, in their view, of an underlying disorder – but as a patient, I feel truly lucky to be living at a time of so much amazing research. While I would never wish diabetes on anyone, I am grateful to these scientists for their vision, dedication, and sacrifice, and of course I always feel in debt to the clinicians and educators who are committed to the cause.

Speaking of ADA, I'd like to invite you to attend a soiree at our home on the evening of Friday, June 6. Our home is rather close to the Moscone Center; please send an RSVP if you can make it and we'll provide you with directions. We'll be raising our glasses to good work being done in diabetes and will relish talking diabetes – thanks to all for working toward the same end. I look forward to seeing you at ADA and talking diabetes out of the office with our team and with yours.

We hope you love this issue. Mark Yarchoan and I were privileged to interview NIH diabetes guru Dr. Judith Fradkin where she discussed, among other things, health care economics, ACCORD trial data, and cut backs in special funding for type 1 diabetes. In addition to all the diabetes updates, we have a special preview of ADA – what not to miss in San Francisco next week.

And on that note we really hope you don't miss our Second Annual TCOYD benefit – come listen to diabetes experts Drs. Steve Edelman, Wendell Cheatham, Anne Peters, Bob Henry, James Gavin, and Eugene Wright riff on GLP-1, CGM, DPP-4, PTP-1B, 11b-HSD1, SGLT-2, CB-1 antagonists, and GPCR modulators. Oh, and insulin and insulin delivery. $175 person special DCU rate will be good through Monday – thanks so much to everyone who has signed up at www.supporttcoyd.org. Amazing support.

Last, I'm personally so excited that so many of you are coming to San Francisco (and excited to see everyone that lives here!) and hope that our team's "CC ADA guide to five action-packed days, 200 exhibits, and 2840 Poster or Oral Presentations" is helpful as you plan your time in our fair city by the bay.

Sincerely,

Kelly L. Close

Major Headlines

Novo Nordisk files once-daily GLP-1, liraglutide, in EU and US – *page 5*

ADA Preview: Your guide to five action-packed days, 200 exhibits, and 2840 Poster and Oral Presentations – *page 15*

Interview with Dr. Judith Fradkin, director of the Division of Diabetes, Endocrinology, and Metabolic Diseases, NIDDK – *page 19*

A deeper look at Amylin's pramlintide plus metreleptin phase 2a data – *page 30*

In This Issue

Blogwatch

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

- **May 27:** Get up and dance! PLUS Free diabetes screening for Bay Area residents
- **May 6:** Reporting Bias – Insulin pumping in kids
- **May 2:** Creative ways to look at diabetes on a gray Friday
- **April 25:** What do you mean someone with diabetes can't be healthy?! The New York Times!

Coming soon in DCU...

Our whole team will be covering the eight simultaneous themed tracks of the 68th Scientific Sessions of the American Diabetes Association. In the next issue of *Diabetes Close Up* we will bring you highlights from the conference. Stay tuned!

Diabetes Close Up Staff

Editor in Chief:
Kelly L. Close

Managing Editor:
Mark Yarchoan

Senior Advisor:
James S. Hirsch

Contributors:
Kaku Armah
Daniel Belkin
Michael Chen
Michael Dougan
Jenny Jin
Dana Lewis

1. Quotable Quotes in Diabetes

"As I often say, if you claim to have 100 percent success with islet transplantation, you're either lying, or you didn't wait long enough, or you didn't use enough patients."

— Dr. Camillo Ricordi, head of the Clinical Islet Transplantation (CIT) Consortium, underscoring the difficulty of islet transplantation at the Meeting on Clinical Research Supported by the Special Statutory Funding Program for Type 1 Diabetes Research.

"It is an understatement to say that we were dismayed that analysts so quickly wrote off TI in light of an imbalance in lung cancer occurrence in the Exubera clinical program… It was almost as if we reported an imbalance in lung cancer in our own clinical program for TI."

— Al Mann, CEO of MannKind, differentiating Technosphere Insulin (TI) from Pfizer's discontinued Exubera during the company's 1Q08 earnings call in light of recent evidence suggesting that Pfizer's discontinued Exubera may be associated with lung cancer.

"In the 1970s, I gave a lecture at ADA that described… a cluster of disturbances that surround insulin resistance. My mathematical training was not very comprehensive, but I had remembered that in algebra the term X refers to an unknown quantity. So, naturally, in my lecture I referred to this cluster as 'Syndrome X.' Now 'Syndrome X' is more commonly referred to as the metabolic syndrome – a terrible name in my opinion because some of its components are not metabolic."

— Dr. Gerald Reaven (USA), providing some historical context for the metabolic syndrome in a keynote lecture at the 16th European Congress on Obesity (ECO) in Geneva, Switzerland.

"I don't understand why clinicians worry about making a diagnosis of the metabolic syndrome. It's an arbitrary measure and one of questionable utility. If a patient has elevated LDL cholesterol, you should treat that. If a patient has elevated glucose, you should treat that. I don't care whether a patient has one, two, or three abnormalities – they should all be treated individually."

— Dr. Gerald Reaven (USA), arguing against the use of the metabolic syndrome as a clinical diagnosis in a controversial presentation at the 16th European Congress on Obesity (ECO) in Geneva, Switzerland.

"[Continuous glucose monitoring] is the most frustrating technology I've ever used and yet I don't know how I ever lived without it."

— Dr. Daniel Einhorn, speaking at the 17th Annual Meeting & Clinical Congress of the American Association of Clinical Endocrinologists (AACE) about the benefits of CGM as well as the unique challenges that the technology provides.

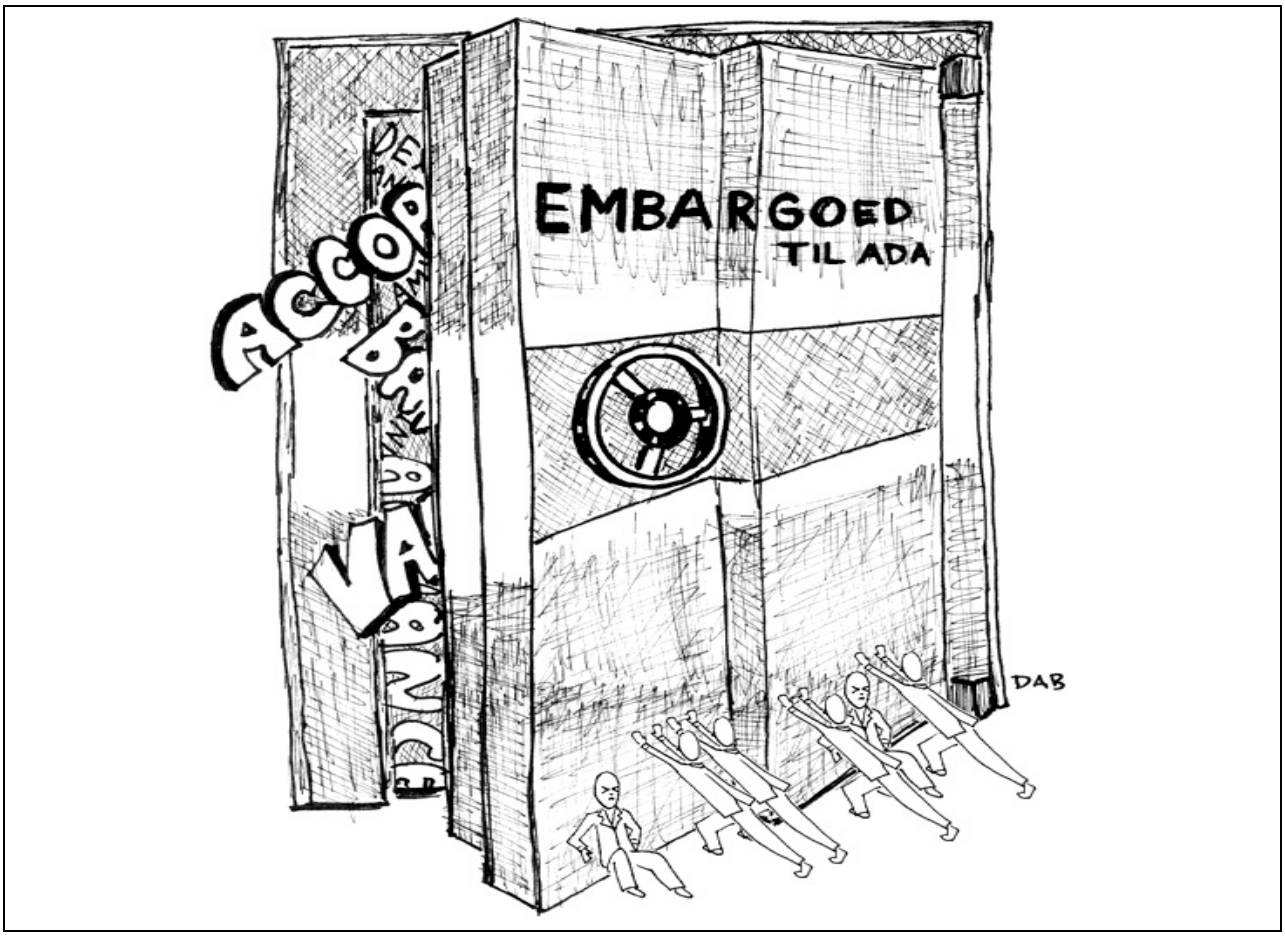
"We're continuing to follow the [ACCORD] patients. Early in the course of DCCT the retinopathy got worse before it got better. I think it's important to try to see what the long-term course is and to see whether there might be some delayed benefit of this period of intensive intervention."

—Dr. Judith Fradkin, director of the Division of Diabetes, Endocrinology, and Metabolic Diseases, speaking about potential follow-up studies for the yet-unpublished ACCORD trial in an interview with DCU that is published on page 19.

"Everybody who was involved with the DCCT knows that it was the diabetes educators who made the intervention work. As soon as the DCCT ended and the patients moved on to the follow up studies, gradually their A1c moved up."

—Dr. Judith Fradkin, speaking about the importance of diabetes education in an interview with DCU that is published on page 19.

2. diaTribe FingerSticks



-by Daniel A. Belkin

3. DCU Company Watch

Novo Nordisk—Liraglutide filed for approval at FDA and in EU – next quarter, Japan!: On May 23, Novo Nordisk announced that it has submitted a New Drug Application (NDA) to the FDA in the US and a marketing authorization approval to the European Medicines Agency for the approval of liraglutide. This timing is right on track and we would look for approval just prior to ADA next year. Impressively, Novo Nordisk plans to file for marketing approval in Japan in the third quarter of 2008 – it will be ahead of Byetta in this market. As a reminder, Liraglutide is a once-daily human analogue of the naturally occurring hormone glucagon-like peptide-1 (GLP-1) which stimulates the release of insulin when glucose levels rise and inhibits appetite in type 2 diabetes patients. How well Lira looks compared to Byetta will be very interesting to see eventually – we'll be eager to see how fasting levels, post-prandial levels, nausea, and weight loss compare (to *really* see this, a head-to-head trial will be necessary).

We are very impressed by the breadth of this filing, and understand it to be the largest diabetes drug submission ever. The clinical program (including the phase 3 "Liraglutide Effect and Action in Diabetes (LEAD)" program for which we have reported top-line data in previous issues of Diabetes Close Up), included 6,500 subjects of whom ~4,200 received clinical doses of liraglutide.

On an exciting note, the drug is being studied in phase 3 clinical trials for obesity and prediabetes indications.

Liraglutide will be the second marketed GLP-1 drug, after Amylin/Lilly's exenatide (Byetta). With Byetta expected to generate well over $800 million dollars in global revenue this year, the GLP-1 market is clearly already significant, but in our view Novo Nordisk's entry into this market will be notable terms of expanding the market. We expect that Novo Nordisk will use its impressive sales force to heavily promote the unique weight-loss aspect of GLP-1 therapy as a significant advantage over DPP-4 inhibitors and other drug classes; this is a message that we believe Amylin/Lilly have struggled to advance to general practitioners. Given that the once-weekly formulation of exenatide in development from Amylin/Lilly will likely not be filed until early or mid-2009, we believe that liraglutide may compete favorably within the GLP-1 market. Relative to Byetta, liraglutide is likely to be associated with significantly less nausea (because it is more similar in molecular structure to native human GLP-1), as well somewhat greater efficacy and weight loss because of its favorable pharmacokinetics. Novo Nordisk is currently sponsoring a post-marketing comparator trial between the two drugs to highlight such advantages. In the eyes of patients, liraglutide's once-daily dosing and intuitive titration may be seen as a significant advantage to Byetta's twice-daily dosing. On the other hand, the efficacy equation may again flip when exenatide once-weekly is approved, given its unprecedented A1c reduction demonstrated in DURATION-1. What remains less clear to us is whether patients will prefer once-daily injection with a smaller needle, or a once-weekly injection with a larger needle. Only time will tell.

- **Alkermes—Exenatide once-weekly is on track:** The Alkermes fiscal 4Q08 earnings call led by CEO David A. Broecker on May 22 was dominated by discussions about Vivitrol and Risperdal Consta. On exenatide once weekly, Broeker said that its development is "on track," and he reminded listeners that DURATION-1 clinical trial data for exenatide once-weekly will be presented at ADA (see ADA preview on page 15 for details). The company expects commercial readiness for the manufacturing of exenatide once-weekly at the end of 2008. During the Q &A, management said that the discontinuation of AIR insulin would not have a significant impact on EPS, and that a final agreement regarding AIR insulin is still being worked out with Lilly.

- **Dexcom—In big vote of confidence, Dr. Jonathan Lord joins board**: This is a major win for DexCom in our view as we remember Dr. Lord's significant contributions to the TheraSense board before Abbott's acquisition of the company. We view Dr. Lord as one of the most innovative thinkers in managed care, particularly in terms of chronic disease and we would look to him to be a major asset to the CGM field in pushing forward the plan to help move reimbursement forward.

- **FivePrime/Pfizer—Oncology and diabetes collaboration:** On May 20, FivePrime and Pfizer announced the initiation of a research collaboration to discover novel protein products and antibody targets for the treatment of oncology and diabetes. By the terms of the agreement, FivePrime will receive an up-front payment and an equity investment from Pfizer as well as three years of committed research funding, while Pfizer will receive exclusive worldwide rights to develop and commercialize products and targets that are discovered during this funded period. Beyond this, terms weren't disclosed but we were glad to see this sign that Pfizer was still pursuing diabetes – we assume it's still working toward simpler therapies than insulin.

  FivePrime has an intriguing discovery approach that we believe could eventually generate first-in-class drugs for diabetes. The company has initially focused screening proteins capable of increasing insulin sensitivity in muscle, as well as proteins that may inhibit hepatic glucose. The company is also developing screens for therapeutic proteins and antibody targets in beta-cell protection and regeneration. Although the company is still very early stage, it has amassed a large

protein library consisting of almost all secreted proteins, peptide hormones, and extra-cellular domains of receptors, many of which are novel proteins and splice variants that are not in the public domain.

- **Medtronic—Medtronic Diabetes hits the $1 billion mark:** Medtronic reported during its fiscal fourth quarter and year end 2008 call on May 19 that Medtronic Diabetes achieved the impressive milestone of $1.02 billion in annual sales, up a whopping 18% from 2007. Although the "organic" growth in pump sales was just over 12% excluding CGM, we think the "real" pump growth is probably closer to 15%, a great mark of health for the pump industry. Fiscal fourth quarter revenue for Medtronic Diabetes was $275 million, up 18% from a year ago and up 7% sequentially. Impressively, CGM was reported to be annualizing at $80 million (compared to $60 million last quarter and $50 million in fiscal 2Q, the first quarter that management began disclosing CGM results). Management noted that growth in the franchise stemmed from continued adoption of pump therapy as well as the rapidly expanding CGM market, which "more than doubled" year over year. Pump growth benefited from sales to new patients and strong performance of the Paradigm RT system outside the US where it was recently launched. Management noted that over the last five years, the franchise has achieved an impressive 17% CAGR, adding that operating margins have improved from low single digits to ~20% during this period. Twenty percent! Also very impressive. Finally, management commented on continuing leverage from the meter co-marketing agreements with J&J and Bayer, noting the positive momentum generated by joint sales calls and co-marketing events.

- **Insulet—Insulin delivery continues to be a hot area:** On May 13, Insulet reported steady/positive first quarter results in a call led by CEO Duane DeSisto. Revenue of $6.7 million rose 31% sequentially from $4.4 million last quarter (growth excludes the $1.2 million favorable deferred revenue impact). Net loss of just under $20 million rose ~27% sequentially and was higher than expected due to higher spending, stemming from a major ramp-up of reps to 49, an addition of 32. There were 1,200 new patients on the OmniPod at the end of 1Q08, bringing total users to somewhere between 5,020 and 5,060 by our math. We believe Insulet continues to expand the market for pumps and that disposable pumps are now in the pump "mainstream" with reps in nearly every state. Production increased to 95,000 pods per month, up 27% from last quarter's 75,000 pods per month and up 58% versus a year earlier – this growth continues on track and will be key to success in becoming gross margin positive in the third quarter and ultimately profitable, which is currently the main challenge facing the company. Insulet closed out the quarter with cash and cash equivalents of ~$73 million.

  We continue to be impressed by Insulet's sales execution and its strides in manufacturing (at least a quarter ahead of the original schedule for higher capacity), and we believe more progress hinges on success in lowering costs through cheaper manufacturing; the progress in China appears on track and success over the next few quarters is critical in order to achieve ambitious operational goals by the end of the year. Future success at Insulet will depend largely on the extent to which the expanded sales force will "catch up" with the higher spending as the additional reps become productive – we are confident on this front as we believe Insulet will continue to further expand the market with its non-traditional, no-tubing pump. We also believe Medtronic and Animas will continue to expand the market for the foreseeable future, and that more physiologic insulin delivery will become more popular as CGM shows the frequency and degree of blood glucose swings experienced patients, even (especially) those with "good" A1cs.

- **Takeda—Actos shows relative strength even as Avandia slides – up 18% for the year; Second-gen PPAR to file in 2010:** On May 12, Takeda reported Actos sales for its fiscal 4Q07 of $809 million (current exchange rates), representing a continued decline from 3Q07 sales of

~$1.03 billion. For the fiscal year ended March 31, 2008, Takeda reported global Actos sales of ~$3.8 billion, up 18%. Actos sales were especially strong in the US, increasing over 41% as compared to the previous year. The drug's relative strength comes at a time when Avandia continues to struggle - global sales of Avandia products fell 56% in 1Q08 versus 1Q07. In the US, it appears that many health care professionals have responded to the safety concerns about Avandia and the extra black box warning the drug received as compared to Actos by switching patients from one to the other – there have also been moves to Actos due to better marketing of lipid benefits. *And*, we believe some doctors have moved away from the TZD class altogether and have moved faster toward insulin, especially long-acting basal insulin, which is widely perceived as the easiest insulin to use, as it is once daily (at least on the label, with Levemir having once or twice daily) and less associated with hypoglycemia and weight gain than many other insulins. We also believe Januvia has been a big beneficiary as another oral that is more tolerable and with metformin, has a similar A1c drop.

Takeda also provided a thorough diabetes and obesity pipeline update during its earnings call. New information to us was the finding that the company hopes to file its second generation PPAR (Actos replacement) in the US and Europe by FY 2010 – this is key in our view because Actos goes off patent in 2011. Nonetheless, we are surprised by Takeda's confidence in this drug given the numerous PPARs that have been dropped in clinical trials due to unexpected toxicities. The company's DPP-4 inhibitor (alogliptin), which was filed in the US in January, continues on in phase 3 in Europe and phase 2 in Japan. During the call, management indicated that it hopes to have alogliptin filed in both regions by FY2010. This should be the next DPP-4 inhibitor approved, and we look forward to seeing more data next week at ADA in San Francisco.

- **Biodel—Discussions are ongoing; waiting for phase 3 data to partner:** During the Biodel 2Q08 call on May 9, management reiterated that VIAject, a new "super rapid-acting insulin" in phase 3 development, remains on track for filing at the end of 2008. The phase 3 trials for VIAject are expected to end in July, and top-line data will be reported in the third or fourth quarter. The phase 3 trials are being conducted in comparison to regular insulin, not insulin analogs, at the request of the FDA – management said that it expects these trials to show a VIAject advantage with regards to safety and, notably, to weight gain. Because the clinical trials for the current generation of rapid-acting insulins were also conducted in comparison to regular insulin, management said that it will be possible to make comparisons between VIAject and its competitors – though we note that from a scientific perspective, there are too many variables to make truly valid comparisons between different trials. Biodel did conduct a small comparison trial (n=16) against Humalog in phase 2, in which statistically significant differences in hypoglycemia rates and PK were shown. In that trial, VIAject became effective after only 13 minutes, compared to 29 minutes for Humalog and 33 minutes for human. We note that the carbohydrate dose was unusually large (120 g) in this trial, and the timing of the insulin administration was immediately prior to the meal. We believe that larger phase 3b superiority trials would be necessary to drive broad clinician interest in the product but if the small Humalog trial can be replicated, we would be very positive about prospects for the company.

  There was no mention of partnerships during the prepared remarks, but in the Q&A CEO Dr. Solomon Stein said that many discussions are ongoing. Nonetheless, he indicated that the company will stick with its longstanding plan of waiting for phase 3 results before partnering. He mentioned that the company is considering three types of partners: 1) Major pharma with insulin products, 2) Major pharma in the diabetes space, and 3) Major pharma "looking for new products that could really put energy behind this."

Biodel reported a net loss for the quarter of $9.6 million, slightly lower than the net loss a year ago. On February 12, Biodel raised an additional $46.8 million through a follow-on public offering of 3,260,000 shares of common stock (at $15.5 per share). Biodel ended the quarter with cash and cash equivalents of $108 million. Management said that this cash reserve will last through 2009.

- **Amylin/Lilly—Modified co-promotion pact for Byetta:** On May 9, Amylin and Lilly announced that they have agreed to a modified co-promotion pact for Byetta in which there will be an increased number of reps promoting Byetta, but the reps will now have multiple drugs in their bag. By the terms of the new agreement, Lilly's retained third-party Cialis sales force will now co-promote Byetta in the US while Amylin's Byetta sales force will co-promote Cialis, an erectile dysfunction drug. Lilly's Byetta sales force will continue to promote Byetta and will not co-promote Cialis. The agreement is not entirely surprising in light of the Amylin 1Q08 earnings call – during that call Amylin management said that it will increase the Amylin sales force by 15% and it spoke about improving its revenue-to-infrastructure ratio and "aligning messages with Lilly." Whether co-promotion will offer a cost-effective way to increase Byetta sales, particularly among PCPs who have been slower than endos to adopt Byetta, remains to be seen – overall the deal seems a positive since probably not much time will be spent on Cialis.

- **Orexigen—Enrollment complete for all four Contrave phase 3 trials:** During Orexigen's 1Q08 earnings call on May 8, management highlighted that enrollment is complete for each of the company's four planned phase 3 trials for Contrave, the company's lead anti-obesity drug that combines the generic compounds bupropion and naltrexone. The trials include: 1) NB-301, one year, ~1,700 patients, assessing safety and efficacy of Contrave in healthy, non-diabetic, obese patients; 2) NB-302, one year, 800 patients, assessing safety and efficacy of Contrave alone or in combination with intense lifestyle modification; 3) NB-303, one year, 1,500 patients, assessing safety and efficacy of Contrave in healthy, non-diabetic, obese patients; and 4) NB-304, one year, 500 patients, assessing safety and efficacy of Contrave in obese subjects with type 2 diabetes.

  For the quarter, Orexigen reported a net loss of $23 million, up from a net loss of $12 million in the same quarter of the previous year. The increase in net loss was attributed to a nearly $11 million increase in R&D expenses pertaining to Contrave phase 3 clinical trials. At the end of the quarter, Orexigen held approximately $33 million in cash and cash equivalents.

- **Vivus—Discussing impact of FDA draft guidance on Qnexa for diabetes:** During the Vivus 1Q08 earnings call on May 8, management spoke about the implications of the FDA draft guidance for Qnexa, the company's phase 3 anti-obesity drug that is a combination of phentermine and topiramate. Management indicated that they believe the new FDA draft guidance paves the way for Qnexa to be approved for diabetes and not just obesity. Vivus conducted a phase 2 study of Qnexa in overweight or obese patients with type 2 diabetes, and the results from this study will be presented at ADA. Vivus also recently initiated a six-month extension study of this original diabetes trial, which we believe represents the company's interest in pursuing a diabetes label for Qnexa. If successful, this approach would be a paradigm shift in the way clinicians (and pharma) approach diabetes treatment – by addressing an underlying cause of hyperglycemia rather than the hyperglycemia itself. We are extremely interested to see Vivus data at ADA.

  Net loss for the quarter was $7.1 million, compared to a net loss of $7.4 million in 1Q07. Total revenue for the quarter was $22.7 million, up from $1.7 million a year ago – this increase was largely attributable to the recognition of $20.9 million in license revenue earned from the prior

sale of Evamist to K-V Pharmaceuticals. At the end of March, VIVUS had cash, cash equivalents and available-for-sale securities of $165 million.

DexCom—Hospital leadership agreement in the works: DexCom reported 1Q08 results on May 8, with total revenue of $1.8 million, up 80% year-on-year and up nearly 20% from last quarter, impressive in our view, and on-target with expectations. Net loss was $13 million, up 19% from 1Q07 and up 6.5% sequentially. Sensor revenue grew 23% over 4Q07 (compared to 39% last quarter). 1Q08 saw 1,200 starter kits sold and a cumulative 1,500 STS users upgraded to the second generation SEVEN. Management expects the number of upgrades to fall off sharply in 2Q08 since it plans to stop production of the STS by the end of the quarter. Overall, we view this quarter's growth quite favorable, given the higher base and given that a very small company has taken on so much responsibility for transformational change in diabetes management. Management discussed recent reimbursement success with Anthem/WellPoint, emphasizing the importance of the next step in the process: negotiating contracts.

On a very positive note, management reported that developments this year on the third generation sensor have yielded a modified sensor with improved performance and convenience without added cost. Additional trials are ongoing this quarter with PMA-S filing expected soon – this filing will be another reflection of DexCom's strong regulatory strategy and execution.

On the hospital glucose monitoring front, DexCom said it expects to complete technical and business due diligence and finalize negotiations with a hospital partner in the next quarter. It sounds like the combined Animas 2020 pump and DexCom sensor integrated product is moving ahead very quickly – this will be exciting for patients and providers.

- **Emisphere—No tug on partnership line:** In a call on May 7 led by President and CEO Michael Novinski, Emisphere discussed progress (or lack thereof) in the development of its oral insulin candidate. Management indicated that they have not found a partner for this product because the data obtained thus far were "inconclusive at best." Emisphere had previously said during its year-end call in February 2007 that it would move forward with the development of the oral insulin product, but that because it is "a drug delivery company rather than a diabetes company," it intends to partner the product with a pharmaceutical company as soon as possible. However, during the more recent call, management appeared quite pessimistic, saying that the probability of short-term success is "highly questionable." They conceded that the data were not matching up with the compatibility criteria for insulin given the product's very narrow therapeutic index. In terms of next steps, they said they would continue to explore "strategic alternatives" and would reveal more in the future. We have not changed our long-held skepticism of oral insulin and further note that with ever-improved insulin formulations and insulin delivery devices, the barriers against taking insulin through traditional means continue to drop. Management briefly mentioned their oral GLP-1 and PYY programs stating that the first studies should be published in June/July this year, with data from the second studies expected this quarter.

- **MannKind—Defending TI safety in the wake of Exubera:** Not surprisingly, a majority of the MannKind 1Q08 earnings on May 5 was devoted to the topic of TI safety in light of the reported imbalance in lung cancer rates in the Exubera clinical trial program last month. CEO Al Mann gave a very impassioned speech and indicated that he was dismayed by the analyst reaction to the Exubera data. He highlighted that as of April 9, there were almost 2,200 patient-years of TI data, accumulated in seven separate clinical trials, and the rate of lung cancer (two cases in total – both smokers, one who had cancer elsewhere that may have spread) has not exceeded the rate of lung cancer that would be expected in a similar, untreated population. Management asserted

vigorously that any potential association between Exubera and lung cancer would not be a class issue, and contrasted the sugar-based carrier compounds used in Exubera with the non-biologically active FTKP carrier used in TI. Nonetheless, management acknowledged that the perception of TI's safety in the eyes of potential partners has been damaged and MannKind has paused all partnership discussions until the publication of phase 3 data later this year. We believe that perception of safety concerns about inhaled insulin will persist until long-term data are available for patients and healthcare providers.

Perhaps as a reaction to analyst concerns about TI safety, management also took the time to highlight MannKind's earlier-stage drug pipeline. Management expressed hope that the mechanism of drug delivery used for TI would become a platform for other drugs, notably GLP-1 and other peptides. MannKind will be reporting the results of its phase 1 clinical trial of inhaled human GLP-1 at the ADA meeting in June. With $250 million raised through an equity financing in October, and an additional $350 million available through a credit facility from Al Mann, the company says it has the resources to continue operations through the end of 2009.

- **Amylin—Initiating phase 2b for combination metreleptin/pramlintide:** On May 5, Amylin reported the initiation of a six-month phase 2b trial of metreleptin (recombinant human leptin) plus pramlintide (analog of the hormone amylin), its lead product candidate for the treatment of obesity. The phase 2b study will enroll 600 patients with BMIs ranging from 27 to 45 and will be completed in mid-2009. We had hoped the phase 2b trial would be longer than six months, as it seemed that weight loss continued to trend downwards quite significantly at the end of the six-month phase 2a trial, and we are eager to know what the weight loss floor is with this combination treatment. The phase 2b trial will test multiple doses of the combination against monotherapy with each hormone as well as placebo. Amylin indicated that the study will "inform the ongoing development of a convenient delivery system for this combination regimen."

  The advancement of this drug combination into phase 2b comes as no surprise given the impressive weight loss and side effect profile seen in phase 2a. In this former trial, patients achieved an average 12.7% weight loss; 89% of patients on the combination therapy achieved greater than 5% weight loss, 56% lost 10% or more, and 28% of patients lost 15% or more.

  Coinciding with the initiation of the metreleptin/pramlintide phase 2b trial, Amylin published the full phase 2a results for the combination in the May 20 issue of the *Proceedings of the National Academy of Sciences* (*PNAS*). Although top-line data for this clinical trial have been available since November 2007, the publication provides new insights about the data and some additional animal data about the combination. We've included a review of this study on page 30.

- **Metabasis—Moving the early diabetes pipeline forward:** During the Metabasis 1Q08 earnings call on May 1, President and CEO Dr. Paul Laikind provided an update on the company's FBPase inhibitor, MB07803. On April 28, Metabasis reported promising top-line phase 2a data indicating that the drug significantly lowered fasting plasma glucose at day 28 versus placebo, and was well tolerated overall. MB07803 is Metabasis's second FBPase inhibitor - as a reminder, the company's first generation FBPase inhibitor, CS917, which was being developed in partnership with Daiichi Sankyo, was dropped after phase 2b results showed a failure to significantly reduce A1c levels in a three-month clinical trial. We believe that phase 2b results will provide better insights as to MB07803's potency. Metabasis hopes to soon form a strategic partnership for the development of MB07803, and to initiate a phase 2b trial in 2009. Metabasis continues to make progress with preclinical development of a glucagon antagonist as well as an AMPK activator for which it has partnered with Merck. Metabasis also said it hopes to recommend a glucagon antagonist product candidate in the second half of the year. Net loss for 1Q08 was $11 million,

roughly equal to last quarter and up from $8.5 million in 1Q07. This quarter, Metabasis secured a venture loan from Oxford Finance and completed a warrant exchange transaction and concurrent private placement, raising $15 million. The company has $36.4 million in cash and cash equivalents compared to $42.4 million at the end of 2007.

- **Novo Nordisk—Insulin analogs continue to drive diabetes care growth:** Novo Nordisk reported solid 1Q08 earnings on April 30, with diabetes care sales of 7.843 million DKK ($1.64 billion), up 10% year over year (16% in local currencies), and down slightly (1.8%) from 4Q07. As in past quarters, sales of insulin analogs drove overall diabetes care growth, increasing 25% year over year (33% in local currencies). In local currencies, global sales of NovoRapid (Novolog), NovoMix, and Levemir for the quarter were 1.8 billion DKK (~$376 million, up 15%), 1.2 billion DKK (~$251 million, up 18%), and 0.8 billion DKK (~$167 million, up 70%). International sales continue strong, with China up 40%, Brazil up 20%, and India expected to be up 20% for the year. Impressively, 1Q net profits grew 28%. Novo Nordisk's market share growth against Sanofi and Lilly appears to have flattened a bit, as measured by volume. Some of this is due to increased competition and increased investment by competitors – management said this in a very interesting Q&A (see below) where the competitive outlook was summed up succinctly with CEO Lars Sorensen noting that the cost of business is going up.

  On the R&D front, Novo Nordisk's liraglutide for obesity phase 3 trial will begin by year-end; in Q&A, management noted that the trial must be designed so that Novo Nordisk can file for an obesity indication after the first year of the study. In the same breath it mentioned plans for pre-diabetes and diabetes prevention and we look forward to hearing more about this in the future. Phase 2 data will be shown at the Obesity Society meeting (formerly NAASO) in Phoenix this fall. Also in R&D, management announced that Novo Nordisk has terminated all pulmonary delivery activities, namely inhaled long-acting insulin and inhaled GLP-1 – it had already terminated its short-acting inhaled program some months back. Sørensen indicated that the decision was a reaction to the recent reports that Exubera may have caused lung cancer. We also believe management saw the value in sticking to its key area of focus and potentially recognizing from a risk/benefit perspective that the funds could be better used on the GLP-1 front. On that topic, Novo Nordisk reaffirmed that it expects to file for regulatory approval of liraglutide in the US and in Europe "before the end of 2Q08" and indeed it was filed last week. Filing in Japan is expected in 3Q08. Global phase 3 data for liraglutide will be presented at the ADA meeting in San Francisco. A final highlight of the call was that management noted that a Byetta vs. liraglutide trial will be out later this year – this will likely bode well for Novo Nordisk if once-weekly exenatide isn't submitted until the end of 1H09 – the earlier that gets filed, the less important this trial will be overall as we expect once-weekly exenatide has potential to be a truly transformative therapy.

- **Sanofi—Envisioning Lantus as the top grossing diabetes drug:** In a call on April 29 led by Hanspeter Spek, EVP of Pharma, Sanofi-Aventis reported Q1 Lantus sales of €557 million (~$870 million). This reflects robust year-over-year growth of ~31%, similar to last quarter's robust growth. Quite something for a single injectable drug – what a roll it continues to be on. The result broken down was US sales of €327 million ($510 million), up 36% versus a year ago, and European sales of €168 million ($262 million), up 15% from a year ago. The "Rest of World" category came in at €62 million ($96.8 million), up 59%. The Lantus SoloSTAR insulin pen was mentioned as supporting growth of Lantus sales.

  Of note during the call, management noted that data from two Lantus/Apidra trials, TULIP and GINGER, would be unveiled at ADA 2008 and at EASD 2008, respectively. TULIP compares two or more oral antidiabetic agents (OADs) with lifestyle management to two or more OADs with

Lantus in a population of type 2s with a baseline A1c of 7-8%. A look at Lantus in a presumably younger population should prove interesting. There was no news during the call on rimonabant or phase 3 progress for AVE0010, the company's GLP-1 candidate, nor were any metrics presented for Apidra. The biggest "ah-ha" of the call to us was hearing more on management's Lantus vision – the aim is to move Lantus from the top-selling insulin to the top-selling antidiabetic agent, overtaking Takeda's Actos – an ambitious move but certainly a goal Sanofi could reach and one that highlights the intensity of the company's aspirations in diabetes.

- **Medco—Complaints about the CMS competitive bidding process:** A discussion regarding the CMS bidding process dominated the Medco 1Q08 earnings call on April 29 led by CEO Richard Rubin. Management expressed dissatisfaction that PolyMedica, Medco's recently acquired mail-supply diabetes franchise, failed to win a bid in the ongoing CMS competitive bidding pilot program. Although this will not have a serious impact on earnings in the short run because the CMS pilot program affects only 7-8% of the Liberty base and because PolyMedica placed its tender before being acquired by Medco, there is the potential for greater impact moving forward if the pilot performs well in the eyes of CMS. Management cited a few specific complaints about the CMS pilot program. In particular it was disappointed that the bids appear to have been allocated based on business plans without the long-term experience and know-how that companies like Medco/PolyMedica bring to the table (i.e., it was sold to the lowest bidder, without other considerations). Apparently three out of the four top players in the mail-order space were excluded from the awards. Given the paucity of knowledgeable long-term players in the field participating in the pilot program, management expressed the sentiment that the pilot program with the current winners would degrade the quality of the mail channel and eventually drive business back to retail. While lower bids are good for the taxpayer, we imagine that others succeeded in making lower bids in part by not investing in areas such as support and education, which is unfortunate for diabetes patients. Ironically, management revealed that a number of the winners in the bidding process contacted Medco shortly after they had been notified, inquiring if Medco would be interested in buying them. Other winners allegedly tried to outsource to Medco.

- **Medronic/JNJ—OneTouch Ultralink Meter approved in US:** On April 28, Medtronic and J&J announced FDA approval of the LifeScan OneTouch Ultralink meter, which can wirelessly transmit blood glucose data to Medtronic Diabetes insulin pumps and continuous monitoring systems. The OneTouch Ultralink is now the only meter in the US exclusively certified by Medtronic for wireless transmission of blood glucose data to the Paradigm and Guardian. Medtronic customers in the US are expected to receive their new meters by June 30, 2008. The company is working to shift its entire customer base to the new meter at no cost to "eligible US customers," presumably everyone with a Medtronic pump. All new customers who order the Paradigm or Guardian systems will also receive the new meter at no extra cost.

  The US partnership between J&J and Medtronic was first announced in May of 2007. As we previously noted, we think it is impressive that Medtronic forged two separate meter/strip partnerships with J&J (US only) and Bayer (international). Although J&J and Medtronic technically compete on the insulin pump front, we believe there is great potential in this market and that both companies (and Insulet) will continue to expand the market for some time. Only about 23% of type 1 patients in the US wear pumps currently. We believe this will continue to increase with the advent of simpler, easier, and better pumps as well as continuous monitoring options. As such, good marketing and good partnerships will help the entire industry, in our view.

  Easier and more accurate bolus dosing are two features emphasized as important advantages of having the Ultralink meter. Wireless transmission of blood glucose data to the Bolus Wizard calculator or to the Guardian for calibration will make for fewer steps for patients currently

completing these steps manually. While the older Paradigm Link meter also had the wireless feature, not all patients used the meter either due to lack of insurance coverage or reliability issues. Although it is possible some patients will not have coverage for the LifeScan OneTouch strips, LifeScan's overall coverage is extremely broad.

- **Bayer ContourLink approved in Germany and Canada**: Bayer announced in May that it launched the ContourLink in Canada; it also launched this meter in Germany in February and other launches are planned for the coming months. As noted earlier, Bayer's Contour meter is the meter that will be given with Medtronic Paradigm pumps internationally – this deal was a big win for Bayer last year as it gained access to high-frequency testers abroad. Bayer has a strong presence in markets throughout Europe, Latin America and Asia.

- **Bayer—Excellent diabetes care results:** Bayer reported its 1Q08 results and had a solid quarter in Diabetes Care for its largest products. Overall sales reached ~ $360 million using current exchange rates. This represents 6.6% growth on a currency-adjusted basis and although relatively flat on a reported basis, growth was strong for the key products, particularly the Contour blood glucose meters that are phasing out the Elite BG meters (lower Elite sales pulled down overall sales growth). Contour sales rose 21% (~28% on a currency adjusted basis) at ~$200 million) from ~$170 million last year same time. After a successful launch in 1Q07, the Breeze line was down 21% at ~$50 million from 1Q07. Management emphasized during Q&A – as well as during the call - that results for Breeze sales should be considered in light of the tough comparison with a strong 1Q07 when the product was launched. Responding to a question about whether disappointing Ascensia brand sales overall were due to the same delays in orders being experienced by competitors, management reiterated its belief that they were doing better than key competitors, expressing confidence that Bayer would have another strong year in diabetes.

- **Enteromedics—On track for PMA submission to the FDA in mid-2009:** On April 23, the development-stage medical device company EnteroMedics reported a net loss of $8.5 million for 1Q08, with R&D expenses of $6.2 million. As a reminder, the company is developing a treatment called the "Maestro System" that blocks signals to the vagus nerve (a therapy they term "VBLOC") using high frequency, low energy electrical impulses. EnteroMedics did not hold a 1Q08 earnings call, and the earnings information was disseminated in what amounted to one of the shortest press releases we have ever come across. The main news was that the EMPOWER pivotal trial is on track to complete enrollment by the end of June. This study will enroll 220-300 patients at 15 sites in the US and Australia, and data from this trial will be used to support the PMA of the Maestro System. The company plans to submit the PMA to the FDA in mid-2009 for commercialization in early 2010. EnteroMedics has cash, cash equivalents and short-term investments of approximately $47.9 million. Assuming that the current cash burn rate of $8.5 million per quarter will continue through next quarter and then drop with the completion of the EMPOWER study, the company should have sufficient cash to wait until EMPOWER results are unblinded in mid-2009. It would then have to rely on positive results to further validate VBLOC technology and raise more capital.

- **GSK—Another tough quarter for Avandia, but still annualizing at $3 billion:** CEO JP Garnier began his GSK Q108 presentation on April 23 by referencing Avandia weakness. Avandia sales for the quarter declined 56% as compared to 1Q07, from £414 million to £191 million. This was a decline from 4Q07 sales of £231 million. The US drop in Avandia sales was the largest in percentage terms, down 66% from the same quarter a year earlier. European Avandia sales were £54 million, down 14%, while international sales reached £38 million, down 44%. On a positive note, there was some growth in the EU for the franchise with Avandamet – in general, combining drugs with metformin is an important trend.

Will Avandia sales turn around? Garnier put forward that Avandia sales reached a near equilibrium for the final eight weeks of the quarter. Avandia now holds a stable 4% share of OAD market, clearly down from the peak years of TZD use before Dr. Nissen's meta-analysis and the subsequent media storm. Garnier said that it is too early to tell if Avandia will become a growth driver again, and he said that if an Avandia turnaround happens, it will likely begin in the next two to five months.

On the Alli front (over-the-counter orlistat), GSK cryptically reported a disappointing $9 million in sales in its quarterly report (assuming this is the "weight management" line item under the consumer division). As Alli was launched in the second quarter of 2007 and as sales since then have declined, we are not sure what the future of Alli will be. This is disappointing given the very big DTC launch and early results for this OTC product. As a reminder, fourth quarter '07 Alli sales were £40 million, up 33% from £34 million in 3Q07 and £76 million in 2Q07. As a reminder, total Alli sales in 2007 were £150 million in 2007: £40 million in the fourth quarter, £34 million in the third quarter and £76 million in the second quarter (big stocking presumably). There was no pipeline news or updates regarding the Sirtris acquisition.

- **BD—International diabetes care drives growth:** On April 22, in a call led by President and CEO Edward J. Ludwig, BD Diabetes Care reported 2Q earnings of $187 million, reflecting 9.5% growth over F2Q07 – 4.6% sans FX – and flat sequentially. Diabetes Care was once again pegged as one of the growth drivers in the quarter, unsurprising as we think insulin pen needles in particular are doing well. US sales reached $97 million, flat from F2Q07 and down 1.7% from the previous quarter. Management pointed to the loss of a contract with the Veterans Health Administration last year as hurting US sales in Diabetes Care and announced the positive news that this contract had been regained this quarter. Management was confident in saying that growth going forward would be similar to or greater than 9% growth seen last quarter – very impressive. Outside the US, BD Diabetes Care posted sales of $90.6 million, up 23% (11.7% sans FX) from same period last year and flat sequentially.

—by Kaku Armah, Kelly Close, Jenny Jin, Dana Lewis, and Mark Yarchoan

4. ADA Preview: A Guide to Five Days, 200 exhibits, and 2840 Oral or Poster Sessions

June 6 - 10, 2008 • San Francisco, CA • http://professional.diabetes.org/

More than 13,000 people are expected to crowd into San Francisco's Moscone Center to attend the 68th Scientific Sessions of the American Diabetes Association. While the ADA Annual Session has long been the highlight of the diabetes calendar year, we believe that this year's ADA will be particularly exciting and data rich, featuring the presentation of three large cohort trials examining the relationship between intensive glucose control and cardiovascular disease: ACCORD, ADVANCE, and the VADT Study. Below is a list of must-see posters and oral sessions, as well as some background on ACCORD, ADVANCE, and VADT to maximize your ADA visit.

A Dozen Must-See Oral Sessions

- **ACCORD Trial Study Results.** ACCORD is a ~10,000 patient trial comparing cardiovascular outcomes of type 2 diabetes with high cardiovascular disease risk targeting an A1c of < 6.0% or an A1c of 7.0% to 7.9% Patients in the study were treated and followed for four to eight years (mean of ~5.6 years) at 77 clinical sites within the United States and Canada. As reported previously this year, the intensive treatment arm of the trial was halted 18 months ahead of its expected completion date after the Data Safety and Monitoring Board (DSMB) found that the intensive

treatment arm had 25% more deaths than the standard treatment arm (see DCU #77 - February 2008 for details). As this was the opposite result from what was expected, clearly we all want to learn more about the cause(s) of the increased mortality. We hope to get some answers in this session, although we expect that the session may raise more questions than it answers. In the initial press release the organizers noted that the increased mortality was not caused by any specific drug agent or increased diagnosed hypoglycemia – we will be eager to learn more. We expect NEJM piece on ACCORD before this talk. Presenters: *Dr. Sue Kirkman, Dr. John Buse, Dr. Denise Simons-Morton, Dr. David Goff, Jr., Dr. Faramarz Ismail-Beigi, Dr. Hertzel Gerstein, Dr. Robert Byington, Dr. Michael Miller, Dr. Jeffrey Probstfield, and Dr. Richard Grimm, Jr.* Time: *Tuesday June 10 at 7:30 AM, Clinical Diabetes/ Therapeutics track.*

- **Advance Trial Study Results**. ADVANCE is an 11,140-patient international study on the effect of intensive blood pressure lowering and tight glucose control in high-risk hypertensive or non-hypertensive individuals with type 2 diabetes on the incidence of vascular diseases. Shortly after the ACCORD trial was halted, the organizers of ADVANCE asked the study's Data Monitoring and Safety Committee to make a statement about whether intensive blood glucose lowering was associated in the study with increased mortality based on interim study data. The resulting statement, released by the University of Sydney's George Institute for International Health that is running the study, found that the study "provide[s] no evidence that intensive treatment to lower blood glucose (sugar) increases risk of death" – apparently in disagreement with the ACCORD press release, though the study methods and patient populations were somewhat different. We look forward to seeing the full ADVANCE results, and we hope for some further clarity on the association between tight glycemic control and cardiovascular disease risk. Presenters: *Dr. David Nathan, Stephen MacMahon, Dr. John Chalmers, Dr. Anushka Patel, Dr. Bruce Neal, Dr. Mark Cooper, Dr. Michel Marre, Dr. Simon Heller;* Time: *Friday June 6 at 2:00 PM, Clinical Diabetes/ Therapeutics track.*

- **Glycemic Control and Cardiovascular Outcomes - The VA Diabetes Trial.** The Veteran's Affairs Diabetes Trial (VADT) randomized ~1,740 US veterans to either intensive therapy (A1c goal <6%) or conventional therapy (A1c goal <8%). As with ACCORD and ADVANCE, a variety of antidiabetic agents were used in the trial including glimepiride, metformin, rosiglitazone, insulin and other agents. Very little information has been published about this trial, and we are eager to see how the data from this trial compares to ACCORD and ADVANCE. Presenters: *Dr. Vivian Fonseca, Dr. Carlos Abraira, Dr. Thomas Moritz, Dr. Peter Reaven, Dr. William Duckworth, and Dr. Vivian Fonseca.* Time: *Sunday June 8 at 4:15, Clinical Diabetes/ Therapeutics track.*

- **Panel Discussion: Glycemic Control and Heart Disease - Implications for Clinical Practice.** If the ACCORD, ADVANCE, and VADT sessions leave you feeling dizzy, we recommend that you attend this panel session at the very end of ADA. We hope that the expert panelists will provide possible explanations for the likely conflicting data produced by the three trials studying glycemic control and cardiovascular disease. Gear up for this one, what an impressive set of experts! Chair and panelists: *Dr. Harold Lebovitz, Dr. Robert Rizza, Dr. Robert Sherwin, Dr. Rury Holman, Dr. Sue Kirkman, and Dr. Eberhard Standl;* Time: *Tuesday June 10 at 9:30 AM, symposium.*

- **Late Breaking Clinical Studies: Exenatide Once Weekly Elicits Sustained Glycemic Control and Weight Loss Over 52 Weeks.** As we have written, Exenatide once-weekly is a potentially transformational drug in development, and we are eager to see year-long data for the drug. In a 30-week comparator trial against Byetta, once weekly exenatide was associated with a remarkable 1.5% A1c drop on average; more than 75% of subjects reached the ADA target A1c of

7%, while approximately half reached an A1c of 6.5%. We will also be judging the audience reaction to this presentation – we believe that the drug's efficacy, weight loss, and safety profile (likely little or no hypoglycemia) will turn heads. Presenter: *Dr. John Buse*; Time: *Monday June 9 at 4:30 PM, Clinical Diabetes/ Therapeutics track.*

- **329-OR: Efficacy and Safety of Dapagliflozin in a Dose-Ranging Monotherapy Study of Treatment-Naïve Patients with Type 2 Diabetes.** This oral session will provide 12-week clinical data for dapagliflozin, the most advanced SGLT2 inhibitor in development by BMS/AZ. This presentation is especially notable because it is likely to give a first snapshot about the potential for this drug class. SGLT-2 (sodium glucose transporter- 2) is a protein expressed primarily in the kidney that prevents the excretion of glucose in urine. By inhibiting this protein, SGLT-2 inhibitors may increase glucose excretion in urine and thereby lower blood glucose. We will be paying particular attention to the side effects, as some experts have previously expressed concern that SGLT-2 inhibition will lead to increased urinary tract infections. Bacteria that can live around the entrance to the urinary tract cause these infections, and the high levels of glucose passing through the urinary tract may help these bacteria grow. We will also be looking for evidence of weight loss, as SGLT-2 inhibition should lead to the excretion of anywhere from 100-300 calories per day. Presenter: *Dr. James List*; Time: *Monday June 9 at 4:30 PM, Clinical Diabetes/ Therapeutics track.*

- **39-OR: Continuous Glucose Monitoring Results from the Treating to Target in Type 2 Diabetes (4-T) Trial.** The 4-T trial was an open label trial that randomized type 2 patients on metformin and sulfonylureas to one of the following three insulin regimens: a) long acting analog (Levemir) once daily (increase to twice-daily as needed), b) prandial rapid acting (NovoRapid) three times daily, and c) pre-mixed biphasic (NovoMix) twice daily. The three-year trial had interim one-year data presented at the EASD meeting last year in Amsterdam. The interim data was not terribly positive for insulin in our view; only 8% of subjects in the basal arm, 24% of subjects in the prandial insulin arm, and 17% of patients on biphasic insulin achieved an A1c of 6.5% or less. The ADA presentation should be particularly interesting since it will be the first data presented on CGM use in this trial. We hope that it will shed some light on whether it was the regimen, adherence to the regimen or some other factor that prompted the disappointing interim results. Presenter: *Dr. Melanie J. Davies*; Time: *4:15 PM on Sunday June 8, Clinical Diabetes/ Therapeutics track.*

- **390-OR: Effect of VI-0521 (Phentermine and Topiramate) in Type 2 Diabetes.** This oral session will provide the results from Vivus's 28-week study of Qnexa (combination phentermine and topiramate) in approximately 200 subjects with type 2 diabetes (the OB-202 study). The study is likely to indicate whether Qnexa, which is being developed for the treatment of obesity, may obtain a secondary indication for diabetes. Presenter: *Dr. W. Timothy Garvey*; Time: *Tuesday June 10 at 7:30 AM, Clinical Diabetes/ Therapeutics track.*

- **Delay in Progression to Type 2 Diabetes in Patients with Cardiovascular Disease Treated with a Novel Anti-Inflammatory, Anti-Oxidant, AGI-1067: Evidence from ARISE.** This late-breaking oral session will provide data from AthroGenic's lead anti-inflammatory drug, which was first developed by the company in partnership with AstraZeneca as an anti-atherosclerotic agent. In phases 1 and 2, the dug was well tolerated and showed some positive effects on plaque volume; however, the drug proved to be ineffective at preventing cardiovascular events in its pivotal phase 3 trial. Given the increased focus on inflammation as an underlying cause of insulin resistance and diabetes, we are eager to see what long-term effect this drug had on preventing diabetes. The results have implications not only for AGI-1067, but for

other classes of drugs that may work through reducing inflammation. Presenter: *Dr. Jean-Claude Tardif*; Time: *Monday June 9 at 4:30 PM, Clinical Diabetes/ Therapeutics track.*

- **229-OR - Is an Automatic Pump Shut-Off Feature Safe for Children with Type 1 Diabetes? An Exploratory Analysis with a Closed-Loop System.** We believe that the transition to a closed-loop system will likely be bridged by semi-closed loops, such as a system featuring automatic pump shut-off. We are eager to learn about how feasible such a system is given current CGM and CSII technology. Presenter: *Dr. Jay Sosenko*; Time: *Sunday June 8 at 4:15 PM, Clinical Diabetes/ Therapeutics track.*

- **230-OR - Preventing Hypoglycemia Using Predictive Alarm Algorithms and Insulin Pump Suspension.** As with the session above, we hope that this presentation will shed some light on the near-term feasibility of semi-closed loop systems. Furthermore, the presenter and lead researcher of the study Dr. Bruce Buckingham is always a pleasure to hear speak. Presenter: *Dr. Bruce Buckingham;* Time: *Sunday June 8 at 4:15 PM, Clinical Diabetes/ Therapeutics track.*

- **330-OR: Rimonabant Improves Glycemic Control in Insulin-treated Type 2 Diabetes: The ARPEGGIO Trial**. ARPEGGIO is a 48-week phase 3 study examining the use of rimonabant vs. placebo on top of insulin in ~370 subjects with type 2 diabetes. Since we are assuming the strategy with this drug is (in part) to combine it with a DPP-4 inhibitor in development, we're especially eager to see results in a type 2 diabetes population. Presenter: *Dr. Priscilla Hollander*; Time: *Monday June 9 at 4:30 PM, Clinical Diabetes/ Therapeutics track.*

Must-See Poster Presentations

- **505-P:** Liraglutide, a Once-Daily Human GLP-1 Analog, Significantly Improves Beta-Cell Function in Subjects with Type 2 Diabetes; *Authors: David Matthews, Michel Marre, Tu Duyen Le-Thi, Milan Zdravkovic, Rafael Simó*

- **517-P:** Once-Daily Saxagliptin Monotherapy Improves Glycemic Control in Drug-Naïve Patients with Type 2 Diabetes; *Authors: Ulio Rosenstock, Carlos A. Aguilar-Salinas, Eric Klein, James List, Mary Beth Blauwet, Roland Chen*

- **446-P:** Alogliptin Monotherapy Improves Glycemic Control in Patients with Type 2 Diabetes; *Authors: Ralph Defronzo, Penny Fleck, Craig Wilson, Qais Mekk*

    - **See Also:***444-448 –P: (Phase 3 data of alogliptin plus insulin, sulfonylurea, metformin, and pioglitazone)*

- **81-LB:** The Impact of Malglycemia on Mortality and Infection for Patients Undergoing Allogenic Hematopoietic Stem Cell Transplants; *Authors: Irl B. Hirsch, Marilyn Hammer, Ted Gooley, Michael Boeckh, Paul O'donnell, Corey Casper*

- **499-P :** INT131: A Selective PPAR□ Modulator (SPPARM) for Type 2 Diabetes Mellitus (T2DM); *Authors: Fredrick Dunn, Linda Higgins, Alex Depaoli*

- **60-LB:** No Effect of GLP-1 on Human Brain Glucose Delivery During Hypoglycaemia; *Authors: Susanne Lerche, Birgitte Brock, Joergen Rungby, Hans Erik Boetker, Kim Vang, Jens J. Holst, Albert Gjedde, Ole Schmitz*

- **61-LB:** Pioglitazone Enhances Beta Cell Function in Normal Glucose Tolerant, Insulin Resistant, Subjects; *Authors: Elisa Choi, Jose Canales, Roxanne Aquino, Gaytri Scheel, Eli Ipp*

- **221-P:** A Pilot Study of 10-Day Use of the SEVEN Continuous Glucose Monitoring System; *Authors: Satish K. Garg, Kelly Jones, Mary K. Voelmle, Ramachandra G. Naik, Samuel L. Ellis*
- **540-P:** Small Molecule Activators of SIRT1 as a Therapeutic Approach to Type 2 Diabetes: The Identification of SRT100 as a Clinical Candidate; *Authors: Robert B. Perni, Chi B. Vu, Jean E. Bemis, Pui Yee Ng, Jeremy S. Disch, Joseph J. Nunes, Jill C. Milne, David P. Carney, Amy V. Lynch, Philip D. Lambert, David J. Gagne, Siva Lavu, Walter J. Lunsmann, Peter J. Elliott, Michael R. Jirousek,*
- **1433-P:** AC164209, a Peptide Hybrid Linking a GLP-1 Agonist with an Amylin Mimetic, Exerts Anti-Diabetic and Weight Loss Properties; *Authors: Christine Mack, James Trevaskis, Chris Soares, Chengzao Sun, Diana Lewis, Aung Lwin, Carolyn Jodka, Krystyna Tatarkiewicz, Bronislava Gedulin, Julie Wilson, Michael Hanley, Soumitra Ghosh, David Parkes, Bruce Forood*
- **1196-P:** Glycemic Control is Strongly Correlated with Clinical Outcomes for Diabetic Patients Admitted to Non-Critical Care Internal Medicine and Family Practice Hospital Services; *Authors: Michael G. Jakoby, Laura Wardwell, Renato Alcaraz, Nadia Mustafa, James S. Kumar*
- **416-P:** Three years of tight glycemic control with computer software; *Authors: William P. Burgess, Edith Miller, Kelli Dunn, Charlotte, NC*
- **418-P:** Basal insulin-on-board constraint in the setting of closed-loop control; *Authors: Howard Zisser, Eyal Dassau, Wendy Bevier, Lois Jovanovic, Francis J. Doyle III, Santa Barbara, CA*

—by Mark Yarchoan

5. Interview with Dr. Judith Fradkin, director of the Division of Diabetes, Endocrinology, and Metabolic Diseases, NIDDK

Dr. Judith Fradkin is the director of Division of Diabetes, Endocrinology, and Metabolic Diseases(DDEM) within the National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK) of the National Institutes of Health (NIH). Dr. Fradkin began working at the NIDDK in 1984 as chief of the Endocrinology and Metabolic Diseases Program Branch. She has a biochemistry degree from Harvard University and a medical degree from University of California at San Francisco. As director of the Division of Diabetes, Endocrinology, and Metabolic Diseases, she oversees more than $600 million in research funding and is one of the most influential people in diabetes. Among other responsibilities, Dr. Fradkin is highly involved in the organization of major clinical trials initiated by NIDDK, such as the recent ACCORD trial. Dr. Fradkin also serves as chair of the Diabetes Mellitus Interagency Coordinating Committee (DMICC), and oversees the appropriation of the $150 million Special Statutory Funding Program for Type 1 Diabetes Research. In a conversation with us, Dr. Fradkin discussed, among other things, health care economics, ACCORD trial data, and cut backs in special funding for type 1 diabetes,

Movements in Diabetes

Mark: Thank you so much for joining us today. Given your important role in diabetes research, we're curious to hear what your vision is for diabetes therapies in the future. Where do you see diabetes ten years from now, and how do you see us getting there?

Dr. Fradkin: The strategy that we have is not to put all of our eggs in one basket. We really don't know where the home run is going to occur, so we're pursuing multiple strategies simultaneously. We're looking both at cell replacement therapy, and we're trying to move forward with the

artificial pancreas type approaches. And I think for the latter, it's going to really be important to try to marry behavioral research with technological advances. I don't know if you just saw, for example, this report that just came out in Pediatrics describing some problems that have come up with adolescents using pumps. This shows us how important it is that as we move forward on the technological front, we also do some of the research to make sure the technologies are useable in real life. I think we just have to be very practical. When you think about what life is like for somebody with diabetes today versus 30 years ago, it's really unbelievable, and we hope to keep moving forward.

Kelly: It's night and day, isn't it?

Dr. Fradkin: Years ago, people were relying on urine tests, and they had no idea what their blood sugar was. We're still not where we want to be, but the progress has been phenomenal. If we can continue to make enormous improvements in the mechanical kinds of approaches to diabetes, I think that's very important. On the other hand, if we are able to in fact intervene immunologically and change the course of this disease, that would be even better. We would love to free people from the burdens of taking care of the diabetes.

Kelly: I especially can relate to what you're saying about diabetes being much easier to manage. Regarding the pediatric piece that came out, we did think it was important for everyone to know about the concerns with pumps. On the other hand, we think it's quite conceivable that a higher percentage of problems are reported with pumps than with MDI.

Dr. Fradkin: I think in general most problems are not reported to the FDA. So if they see reports of problems with pumps, they can assume that many more are going unreported. Don't get me wrong, I'm hugely in favor of pumps. I think the point is that we need to make sure that people know how to use them. For example a study using continuous monitoring provides an example of the practical impact of technology research., Everybody knows that exercise lowers your blood sugar, but I don't think that people really appreciated how long it affects your blood sugar, and that exercise can put you more at risk for nocturnal hypoglycemia if you've exercised much earlier that day, even if your sugar is okay when you go to bed. So I think those kinds of practical observations make a big difference in people's lives.

On Healthcare Provider Economics in Diabetes

Kelly: How do you marry educational efforts with the fact that physician economics and educator economics in the U.S. are so difficult, because they are so poorly reimbursed. Do you think that we will get to better reimbursement?

Dr. Fradkin: If you look at the DCCT, everybody who was involved with the DCCT knows that it was the diabetes educators who made the intervention work. As soon as the DCCT ended and the patients moved on to the follow up study, gradually their A1c moved up. I guess it really depends on your values. How do you value the savings in terms of complications that are going to come from providing people with the support to do something that you know is going to prevent complications in the future? It's really a societal issue, but from my perspective, I think patient education and empowerment is just critical. For diabetes interventions I think it's important to do the kinds of studies the NIH does, where you really follow people long-term. It's the long-term benefits that change the balance in cost effectiveness for intervention. If you're going to take the DCCT and look at the cost effectiveness at the end of six and a half years, you would see one thing. But then when you see the benefits continue to accrue over the next two decades, that makes an intervention all the more cost effective.

On Glycemic Variability

Mark: We've been hearing more lately about the importance of glycemic variability. What do you think about its importance and do you think that there's enough evidence for a long-term clinical trial?

Dr. Fradkin: Well, we've tried to look at this a little bit with regard to DCCT data, where people did have glycemic profiles, on certain days. We tried to look at that versus the A1c, but that data is pretty limited; and I'm not sure you could draw a firm conclusion about the variability. With any question, it's a question of the opportunity cost - you can only do so many clinical trials and so the question becomes, is that the most compelling one. The NIH recently made a huge investment in answering the question of optimal goals for glucose, blood pressure and lipid control through ACCORD. I'd like to study getting people as close to normal as you safely can earlier in the course of disease than in the ACCORD population which already had heart disease or multiple risk factors.

Kelly: It is really competing priorities. On one hand we recognize the need for trials to better understand how CGM and other technologies work, but on the other hand many physicians and payers would say, we're not even going to pay for the technology until we see trial data showing improvements in microvascular and macrovascular problems. The concern we have is that CGM studies might not show much an effect on A1c, and we won't really know what the rest of it means until a glycemic variability trial is done. So would you advocate a glycemic variability study if there was someone else to pay for it – like manufacturers?

Dr. Fradkin: Yes, we do need studies that will help payers make decisions to support this technology. I think the question is, what outcome are you going to look at? It is also important to consider what population should be studied in a study to inform payment decisions for some of these new technologies. An approach that we're considering is a study, for example, in a population that really might benefit from the use of CGM. We recently created a research network to study gastroparesis. This is a really disabling condition where people get huge glycemic variability due to inconsistency of food absorption. We're thinking about potentially looking at CGM in patients who have gastroparesis as a complication of diabetes. That might be a situation where you might really be able to demonstrate some benefits, and that could help get a foot in the door in terms of payment.

On the ACCORD Trial

Mark: Switching gears a little bit, we want to ask about the ACCORD trial. We are looking forward to seeing the full data at ADA, and we assume it will be published soon.

Dr. Fradkin: The paper is in press and yes, there's also going to be, a presentation of some of the ACCORD data from the glycemic intervention at the ADA. There's also going to be a presentation of the VA study, which is a similar study, and also the Advance study. I think it's going to be very interesting to compare the three studies because there are differences in the eligibility criteria and the patient populations that were enrolled.

For me the message is not to extrapolate beyond the population studied. Showing increased mortality with very tight control in people who already have heart disease doesn't mean it's not important to achieve control as close to normal as possible early in diabetes. The DCCT really showed that in type 1 diabetes. With the DCCT we started out with people who are early in the course of their diabetes, before they had heart disease, and we showed that good control made a difference. Now, in the ACCORD trial the subjects either already had heart

disease as evidenced by a heart attack or other problems or they already had multiple risk factors for heart disease. It may be that at different stages of the disease, different interventions are appropriate. Maybe early on controlling glucose before you've got a lot of damage, makes a big difference in preventing heart disease but the effect is different later in the course of the disease. And also ACCORD had a more aggressive protocol, taking the A1c even lower than in DCCT or UKPDS. Also there were different drugs involved that may have had different interactions.

Kelly: The press release was fairly clear saying that the higher number of deaths wasn't due to any specific drugs. Can you how it was possible at that point to know that?

Dr. Fradkin: I think there are limitations in how well you can answer the question because the people in the aggressive group got more of practically every drug. But we looked as hard as we could to identify any particular problem drug or combination, and we couldn't find any one drug to point the finger at. It wasn't a study that was designed to address the safety of individual drugs.

Mark: We're also curious to get your thoughts on the reaction to the ACCORD trial. After the trial was stopped, major newspapers published somewhat sensationalist articles and made it seem like this longstanding belief that lower A1c is a good thing is suddenly thrown out the window. How would you classify the media response to ACCORD? And do you think the coverage was appropriate?

Dr. Fradkin: Well, I think that there was some variability, but by and large I think people were pretty responsible and I think a lot of major media listened to the press conference where we made a lot of experts available. I think the ADA very promptly issued a good statement. I think the NIH issued a good statement. I hope that a lot of people didn't rush out and change their treatment based on this because after all, very few people with diabetes are really at the A1c level that the people in the intensive group in the study were at.

Mark: Given the important data from ACCORD, what do you think are some reasonable follow up studies? What do you think that follow up studies are going to look at specifically?

Dr. Fradkin: We're continuing to follow the ACCORD patients. Early in the course of DCCT, the retinopathy got worse before it got better. I think it's important to try to see what the long-term course is and to see whether there might be some delayed benefit of this period of intensive intervention. Obviously, the blood pressure and the lipid questions are still open. I would like to compare treatment approaches looking at long, term results but it's really difficult in terms of designing clinical trials to try to design them so that things haven't changed by the time you finish the trial. You don't want to invest resources in an approach that will become obsolete. I really think that a major unanswered question for type 2 diabetes is what should be the drug added after metformin if that doesn't control somebody with type 2 diabetes. Metformin is a cheap, safe generic drug. It doesn't cause weight gain. It doesn't cause hypoglycemia. Generally people use metformin as the first therapy, but what's the next thing to add? Is it insulin, an oral agent or exenatide? We don't have a head-to-head comparison, but on the other hand if you're going to fund the head-to-head comparison with the long-term outcome, you have the fear as the funder that maybe by the time you finished the trial, there would be new improved drugs and the whole thing would be irrelevant. So you're trying to weigh, with limited resources, what are the most important questions to ask.

Kelly: Just on that topic, we've certainly seen commercially that healthcare providers respond positively to diabetes medications that are more tolerable, easier to take, that prompt fewer phone calls from patients – Januvia and Lantus would be two that benefit from a "simpler to

take" label, in particular. For us, this is very interesting – a decade ago, pre-Lantus, you didn't really hear about the importance of tolerability, we would argue because there really were no diabetes medications that could be called simple. Most prompted side effects like weight gain, hypoglycemia, edema, fractures, etc. Now of course safety and efficacy are extremely important in judging drugs. But, some of the drugs that have come out more recently are have better side-effects profile, and we'd love your view on the importance of this from a healthcare provider perspective.

Dr. Fradkin: I think a lot of tolerability has to do with education and giving people accurate information about what the side effects might be and also how to minimize the side effects. Metformin, if you start it slowly, if you start it in the evening, if you gradually ramp up the dose, you're likely to have greater tolerability than if you give a patient the full prescription all at once. I think there are a lot of drugs like that where somebody who's experienced can help the person adjust to the medication.

Kelly: It's quite difficult, however, if healthcare providers have little time to advise patients on this – either because they don't have the education themselves (for example, primary care doctors) or because the patient in question has so many co-morbidities that the time allotted to the patient isn't spent on medication training. Then, it's more apt that adherence to medication is lower – and costs are higher in the long run. Do you think this is a real problem and if so, how can this be addressed in our US healthcare system?

Dr. Fradkin: I would love to see all patients have access to diabetes educators who could spend the time to help them with the issues you raise.

Overview of the Special Diabetes Funding Program[1]

Kelly: We attended the recent NIH Special Diabetes Funding Program conference in Washington that you led – we found it both impressive all that NIH has done in diabetes and also daunting in terms of thinking about next steps in research. We hadn't realized that we were hanging on by such a thread. We were wondering if you could just tell us about the history of the special diabetes funding program and what you consider the biggest successes of the program so far.

Dr. Fradkin: I think the special funding has really enabled us to do things on a scale that we would never have been able to do otherwise. And I think, in many cases, we've started things that haven't yet come to fruition. So I'm hoping that the best is yet to come, in terms of the things that we've started. For example, at this point, we're still just totally in the middle of TEDDY (The Environmental Determinants of Diabetes in the Young). We're starting to see the kinds of things that might come out of it from some of the precursor studies that have reported findings with regard to Vitamin D and with regard to cereal exposure. But the precursor studies don't necessarily have the power to really know how strong those associations are between dietary factors and type 1 diabetes for example. We are really looking forward to getting more definitive data from TEDDY.

[1] The Special Statutory Funding Program for Type 1 Diabetes Research is a special program funded by Congress since 1998 that promotes focused, innovative, and clinically-relevant research towards understanding, preventing, and, ultimately, curing type 1 diabetes and its complications. It was originally funded at $30 million a year, but since its inception funding for the program has increased to $150 million per year. It was given a one-year extension in 2008, but its future remains uncertain.

We don't yet have an intervention that stops the immune progression, but we do have agents that slow it and we have the ability now to do trials to try to prevent type 1 diabetes. We now have the ability to try to take something like anti-CD3 into a prevention mode. This has been shown to preserve beta cell function in new onset type 1 diabetes, and Jeff Bluestone has evidence in mice to suggest that it might be more efficacious if you used it earlier in the course of the disease. That's a hugely expensive proposition because you've got to screen tens of thousands of family members of type 1 diabetes patients to find those with autoimmunity who haven't yet developed diabetes. It's not like people who have a disease and present on your doorstep. It's different to try to recruit someone who already has diabetes or somebody who has arthritis and has joint pains versus somebody who's asymptomatic yet may really already have some beta cell loss and not know it. It is a huge and costly effort to find those people to try to intervene early. We've already seen now that we can very accurately identify people who have an 80 percent chance of developing type 1 diabetes over five years. That is important because you wouldn't want to give a potentially toxic intervention to a sizeable number of people who weren't going to get diabetes; so you have to be able to identify that high risk group, and I think we can do that now.

I think we've seen progress in the most important aspects of type 1 diabetes. People are living longer with fewer complications. It's interesting when you look at the Trevor Orchard's Pittsburgh cohort and you see that in people diagnosed in each successive decade since 1950 people are living longer and having fewer complications than those diagnosed ten years before. And we see now that they can't even continue in that study to enroll new people because nowadays people aren't always hospitalized when they develop Type 1 diabetes. Many are treated as outpatients so that they can no longer be identified based on hospital records. That kind shows you how things are moving along.

Kelly: I was really interested to hear you say about the special funding and training career pathway for diabetes, endocrine and researchers- exactly the same problem is happening of course in just regular endocrine and even in CDE. Could you tell us a little more?

Dr. Fradkin: As you may know, we have grants that we give to medical schools so that they have a certain number of training positions, so that they can go ahead and actually recruit people who want to learn to do research. We call these T32 institutional training grants. The advantage of having one of those is that the person knows that they have a job. If you're a person coming out of a clinical training program with a lot of medical school debt, you don't want to hear that you could write a grant that you might or might not get funded. You've got to know you have a job. So if a medical school has a grant so that they can definitely offer a research trainee a position, that helps to recruit people.

Now then, there's a further stage in people's research careers between research fellowship training and really being an independent investigator and that's what we support with career development awards. And for most people those awards are from three to five years, but again people have to write a grant before they are fully developed as independent researchers. And that's a substantial barrier because a lot of people think, "Well, gee, I don't know that I want that uncertainty." That is particularly the case for pediatric endocrinologists because this is a low paying specialty and thus there is a shortage.

So what we did is we made a program that was similar to institutional training grants for research trainees but for pediatric endocrinologists in the career development pathway. This program supports people who are beyond the two years of endocrine fellowship but not quite ready for a junior faculty position. Seven sites got both training awards and career development awards, and this then allowed people to do their training at one of these

institutions and then move for their career development to another one of these institutions. A lot of the people who have come out of this program have now started to get independent academic jobs. We had to stop the career development component of the program because of uncertainty about the special funding – we had the five years of funding but now this last year, we only got the one year of funding – and you can't do a program like that without knowing that you have commitments to support people through the 3 to 5 year course of their career development. But we have continued some of the pediatric endocrinology institutional training grants.

Funding for the Special Type 1 Diabetes Program

Mark: You mentioned that it's hard to plan the distribution of the special diabetes funding given that you only got a one year extension. Could speak about the challenges of trying to budget for the special diabetes program, having no idea what the funding is going to be going forward.

Dr. Fradkin: TrialNet provides an example of how challenging it is to manage research with budgetary uncertainty. In TrialNet many different trials that have been proposed have been approved by the steering committee, but some of these trials will take years to complete. Well, the question is what do you do? Are you cautious? Do you say, we only are going to start as many trials as we know we have money to finish? Or do you say, we're going to keep our fingers crossed that the special funding is going to continue, but then what are we going to do about the people who enrolled in those trials, if the money ends? It's not as if the regular NIH budget is growing. There's a real tension; we're trying to strike a balance between starting some new things but not starting as many as we would if we knew that the money was going to go forward. We could be more aggressive about starting new trials if we had more of a funding road map.

Mark: Would you say that the indeterminate nature of the funding forces encourages shorter term clinical trials and prevents the planning committee from initiating longer-term outcome trials that may span say five or so years or more?

Dr. Fradkin: Yes, it limits our ability to do longer term studies, but we are going forward with some very high priority studies despite the uncertainty. TEDDY is an example of a study we began because we felt it was such a compelling opportunity. That study goes through 2023, so that was a pretty big investment, but there's only so much of that kind of thing that we can do with the indeterminate nature of the funding. This is kind of technical, but under NIH rules, research funding that you receive from grants is supposed to be spent in that year. But with contracts, you're allowed to put in money to fund future years - you sort of buy out the future years in the contracts. What we've been doing is we've been converting some of these studies from grant mechanisms to contracts so that we can prepay some of the out year costs, so that we can finish things we start. But that means that you can start fewer trials. If you have to pay five years worth in one year well, then you can only do a fifth as much research. Also we want to be able to still continue to do some investigator initiated grants because that's always been the traditional strength of the NIH and it's where really new things have come from. We want to pursue creative ideas that individual scientists have and again, you can't really put out a solicitation for one year of funding. Overall, it definitely makes it more challenging and it slows the momentum. I don't think there's any question about that.

Kelly: And what are the implications of slowing the momentum?

Dr. Fradkin: Well, it means we fund fewer grants and we start fewer trials.

Kelly: Can you talk a bit about what you think the longer-term implications are? Even the implications of people going into that field, even both at the endocrinologist level, even probably at the educator level and even at the internal medicine level, if internists sort of think they're the ones who are going to be treating all of the patients for diabetes.

Dr. Fradkin: I think you're absolutely right. I think that people, young people who are starting careers, they want to see secure futures ahead of them. I mean if they see the people that they're working with worry that this money is going to dry out or it's going to end, if the mentors are uncertain abut what's going to happen and are we going to be able to finish the trials, that sends a message to people and…

Kelly: It's daunting.

Dr. Fradkin: Yeah, so I think that it's important for people to see that there's a long-term pathway through for a career in diabetes research.

Kelly: Could you talk a little bit more about NDEP (National Diabetes Education Program) because it sounds like there's a lot of amazing educational work being done there. And I would really love for our readers to learn a little more about that.

Dr. Fradkin: I'm glad you asked. The NDEP was really born after the DCCT when we had this incredibly successful clinical trial and we're saying how are going to get the message out there. NDEP is actually unique among all the NIH education programs in that it's a full partnership between NIH and CDC. I think it's the only education program that is. And that really brings us a lot of strength because the NIH brings the research to the table and the CDC brings the public health apparatus to the table.

So that partnership is very useful, and we've gradually broadened our message. It started off with the message to control your sugar. And then, with all these trials showing that controlling blood pressure and controlling cholesterol was very important also in terms of preventing complications, we extended our message to include comprehensive care. Then after the Diabetes Prevention Program results showed that type 2 diabetes can be prevented or delayed we started a major prevention campaign. We've extended our messages to focus on specific groups of people who may not get the care that they need, such as minority groups. We've had campaigns focused on children, and we just started a campaign for gestational diabetes and children who are born to mothers with gestational diabetes to try to encourage diabetes prevention. It's really steadily expanded; it's only been in existence for 10 years. We have a lot of terrific partners. I think we have really terrific materials on our website, www.ndep.nih.gov.

Kelly: You do. They're amazing. I wondered if you had any specific advice for people who are developing these new technologic products such as CGM, given that you're so grounded in education?

Dr. Fradkin: I think in general what they're trying to do is really take the burden off of the patient and to find the delicate balance between automating things and keeping enough safety features in place so that the automated system doesn't run amok. I see a pretty appropriate balance being struck. I think the progress has really been impressive when you think back even 10 years to where things were. With regard to continuous glucose monitors, that was really still a dream. Now, it's really a reality so now the next step is closing the loop. And we're working with FDA on that.

Kelly: That's so exciting to us – from many perspectives, research, commercial, patient, family. Dr. Fradkin, we so appreciate all of your time, this has been incredible. So our last question - what is it you're most looking forward to seeing at ADA?

Dr. Fradkin: Well, I guess I'm really looking forward to seeing the VA data because that is really closely held. We haven't seen that data at all.

Kelly: We'll see you at that session, Sunday afternoon the 8th! And on that note, we say thank you incredibly for all your time and your commitment to diabetes. Your contributions to the field are truly remarkable and we feel incredibly lucky to have been able to spend this time with you.

Dr. Fradkin: Thank you.

—by Kelly Close and Mark Yarchoan

6. The 45 Percent Solution: A Plan To Prevent Type 2 Diabetes

Let's call it the "45 Percent Solution."

The problem is the epidemic in type 2 diabetes, compounded by the relatively low awareness among at-risk Americans about their own glucose levels. According to one estimate, among adult Americans at risk for developing type 2 diabetes, only 17 percent, or about 22 million adults, know their blood glucose level and what action to take.

Knowing that information, of course, is critical to prevent the disease. So the National Changing Diabetes Program, which was created by Novo Nordisk to improve the lives of diabetic patients, has made that information for at-risk individuals the centerpiece of its latest initiative.

Novo has been joined by other advocacy and business groups to announce a National Diabetes Goal: by 2015, 45 percent of adult Americans who are at risk for type 2 diabetes, or an estimated 59 million adults, will know their blood glucose level and what action to take.

Granted, the "45 percent solution" is not exactly a "solution," but it highlights an emerging consensus about the type 2 epidemic: the only way to get it under control is to prevent new cases. "The diabetes community has said 'yes,' we'll rally around this one point," said Dana Haza, senior director of the National Changing Diabetes Program.

There is no specific plan on exactly how patients will be educated, but the initiative's broad support suggests that the 45 percent goal will be given considerable attention.

Supporters include – big breath now – the American Academy of Physician Assistants, American Association of Clinical Endocrinologists, American Association of Colleges of Pharmacy, American Association of Diabetes Educators, American Diabetes Association, American Medical Group Association, American Optometric Association, Campaign to End Obesity, Center for Health Transformation, Entertainment Industry Foundation, ESSENCE, Food Marketing Institute, National Association of Chain Drug Stores, National Association of School Nurses, National Business Coalition on Health, National Minority Quality Forum, and Revolution Health. And, diaTribe, our own patient newsletter – our surveys show pre-diabetes is major worry for our readers' relatives – and many of our readers actually have pre-diabetes rather than full-blown diabetes.

It's a long list, but it will take a full-court effort to inform at-risk individuals what they need to know and do. It will also take more than a simple "awareness campaign," because most Americans are already aware. According to a Gallup survey of 2,015 people conducted for the National Changing Diabetes Program, almost all Americans (94 percent) consider diabetes a serious health problem, and half said they feel personally affected by the disease.

"Awareness is high, but knowledge and understanding are low," Haza said.

The survey itself was an interesting microcosm of the epidemic. It showed that one in four adults (24 percent) have either been diagnosed by a physician as having diabetes (9 percent) or as being at-risk

for diabetes (15 percent), while another 47 percent of adults report feeling they could be at-risk, even though they have not been diagnosed.

The 45 percent goal was settled on by assessing studies and surveys related to cholesterol testing and awareness, which suggested that cholesterol awareness rose 3.3 percentage points each year. With the current baseline at 17 percent, a more realistic goal would have been to reach 40 percent by 2015, but the program sponsors pushed the goal to 45 percent, in part because of existing efforts to combat obesity and chronic diseases generally.

We're glad they did make the goal so ambitious. Timidity in the face of an epidemic is no virtue.

— by James S. Hirsch and Kelly L. Close

7. Conference Pearls: Gerald J. Friedman Symposium - "Inflammation: At the Crossroads of Obesity and Diabetes"

March 29, 2008 • New York, New York • www.aace.com/meetings/ams/2008/

We attended the Gerald J. Friedman Symposium 55th Annual Scientific Meeting, presented by the American Diabetes Association, on March 29 in New York City. The central topic of the conference was inflammation and its role in obesity and diabetes. In our view, the very existence of a conference specifically about inflammation and diabetes underscores that the presumed link between the two has become widely recognized. Although the precise mechanisms by which inflammation may drive insulin resistance and diabetes are not entirely understood, speakers at the meeting implicated a number of intermediate processes, which are described in detail below. Approximately 200 people were in attendance, and most attendees were MDs or PhDs from the New York area, with a mixture of some fellows, medical students, and nurses as well. There were small booths at the conference from Merck (promoting Januvia/Janumet) and Novo Nordisk (promoting Levemir/NovoLog). Below are our highlights from the meeting.

- **Overall, we believe that this conference reflects a continued growing interest within the diabetes community in the so-called "lipocentric" view of diabetes, and a growing confidence that inflammation plays an important role in insulin resistance.** As a reminder, the lipocentric view of diabetes is that chronic inflammation and ectopic lipid accumulation around the body are the main sources of insulin resistance and are the primary reasons that obesity is associated with insulin resistance. Ectopic lipid deposition in the pancreas may also play a role in beta-cell decay. In review: (1) Caloric surplus → (2) increased adiposity and hyperinsulinemia → (3a) ectopic lipid deposition and (3b) inflammation → (4) insulin resistance + beta cell lipotoxicity → (5) diabetes. Even though all of the presenters operated on the assumption that inflammation and ectopic lipid deposition are the cause of insulin resistance, we note that the precise mechanisms involved are not fully understood, and the presenters seemed to disagree somewhat about which mechanisms may be most relevant. By the end of the meeting it was clear to us that multiple inflammatory pathways may work together to cause insulin resistance and these pathways are only starting to be elucidated. There is a growing consensus that an imbalance between so-called pro-inflammatory (M1) macrophages and anti-inflammatory (M2) macrophages plays a role in the mechanism of inflammation in obesity.
- **Implications on diabetes treatment paradigms**: Although this conference was very focused on basic research, the conclusions of the conference have important implications for the treatment of diabetes in our view. In particular, several presentations indirectly supported the wider use of TZDs because of their role in reducing inflammation and ectopic lipid deposition – interestingly, this was in spite of promoting weight gain. The presentations could also be viewed as supporting treatments that decrease body weight (Byetta), and discouraging the use of

sulfonylureas and insulin (treatments that lower plasma glucose while increasing body weight). We continue to believe that in time the lipocentric view of diabetes will become more recognized within the type 2 patient framework, and with this perspective there will be less of a focus on insulin secretion/A1c and more of a focus on insulin resistance, free fatty acids, mitochondrial dysfunction, inflammation, and other potential drivers of diabetes. This may have implications for drug development, although few specific pipeline drugs were discussed at the conference.

- **Underscoring that ectopic lipid deposition is a driver of diabetes, Dr. Philipp E. Scherer of the University of Texas, Southwestern, showed that fat expansion and proliferation is one way that adipose tissue copes with increased caloric supply** – therefore, in the context of calorie excess, fat expansion is, at least theoretically, a good thing. We point out of course that this isn't so easy to explain to the average patient! Dr. Scherer showed that collagen-6 knockouts have a much better metabolic profile (collagen-6 limits fat-cell expansion). Similarly, transgenic mice with higher levels of adiponectin (which increases fat cell proliferation) show lower fasting glucose in response to a high-calorie diet.
- **Dr. Alan Saltiel of the University of Michigan discussed some of the details of abnormal macrophage activation in obesity.** With obesity comes an increased secretion of MCP-1 and pro-inflammatory cytokines. These signals cause the recruitment of pro-inflammatory M1-polarized macrophages to adipose tissue (and accordingly an increase in inflammatory markers such as TNF-alpha, IL-6, and iNOS). There is also a concomitant decrease in anti-inflammatory M2-polarized macrophages (and IL-10/Arginase).
- **Dr. Steven Shoelson of Harvard Medical School discussed the use of salicylate (an inexpensive generic compound that is chemically very similar to aspirin) for the treatment of type 2 diabetes.** Dr. Shoelson's group has found that in humans, 4.5 g of salicylate a day lowers fasting glucose by nearly 20% - Dr. Schoelson did not provide any details about baseline fasting glucose or A1c, but we do know this was a very small (N=7) study of patients with type 2 diabetes. Dr. Shoelson's group has found evidence that salicylate inhibits the activation of NF-κB, an important transcription factor in the inflammatory response to infection. In early-stage trials, salicylate administration increased insulin sensitivity, increased circulating insulin and first phase insulin, increased energy expenditure, decreased circulating triglycerides, and improved oxidative stress. Dr. Shoelson said that he would like to study this further, but has received no support from industry, "*which is not interested in bringing one of the cheapest drugs known to mankind to market*." It is probably a little much to expect a big pharmaceutical company to invest in drug development of this sort, but we would think the government would be! And, as it happens, the NIH is now funding a 14-week multicenter double masked placebo-controlled dose ranging study in inadequately controlled type 2 diabetes (called TINSAL-T2D). The study is not powered for efficacy (n=282), and the study arms will be unblinded in June. The NIH is also funding a 900-patient study of salicylate for CVD; this had been announced in our IDF 2006 notes (about another talk there by Dr. Shoelson), but there is no further information on it.
- **In a separate part of his talk, Dr. Shoelson showed that obesity has potent effects on the immune cells that typically reduce inflammation.** Usually, inflammation is kept at bay by T-regulatory cells including Fox P3, CD4, and CD25. Dr. Shoelson showed that while normal-weight mice have approximately 50% T-regulatory cells (Fox P3, CD4, CD25), obese mice have only 10% of T-regulatory cells. Therefore, obesity causes a simultaneous increase in pro-inflammatory macrophages, and a decrease in anti-inflammatory macrophages.
- **Dr. Ajay Chawla of Stanford University provided a fascinating evolutionary explanation for the crosstalk between the immune system and metabolism; he**

hypothesizes that inflammation causes insulin resistance because the body is trying to divert glucose from muscle cells to the immune system to fight an infection. When the body is fighting an infection, the immune system has much higher glucose needs. Dr. Chawla explained that this is why people develop increased insulin resistance during infection. When obese people develop insulin resistance from inflammation, this is because the body is acting as if it is fighting an infection.

- **Dr. Chawla explained that there are two types of macrophages - classically activated (pro-inflammatory) or alternatively activated (anti-inflammatory).** These two cell types use different fuels – pro-inflammatory cells rely on glucose, while anti-inflammatory cells use fatty acids as the primary fuel source. Dr. Chawla showed that PPAR-gamma is required for maturation of alternatively activated macrophages. He also showed that macrophage PPAR-gamma knockouts are susceptible to diet induced obesity and insulin resistance.
- **Reviewing data from patients who underwent bariatric surgery, Dr. Karine Clément of Paris VI University showed that weight loss is associated with a decrease in pro-inflammatory macrophages (M1 type), and an increase in anti-inflammatory macrophages (M2 type).** Weight loss also leads to a reduction in numerous inflammatory processes, such as MAPK and cytokine-cytokine receptor interaction, and an increase in many other processes such as oxidative phosphorylation, purine metabolism, and glycosaminoglycan degradation. Some enzymes involved in fat remodeling include MMPs, TIMPS, CATHEPSINS, and GAG.

—by Kelly Close and Mark Yarchoan

8. An In-depth Look at Amylin's Pramlintide plus Metreleptin

Amylin published preclinical and phase 2a data for its lead obesity drug candidate, a combination of metreleptin (recombinant human leptin) plus pramlintide (analog of the hormone amylin), in the May 20 issue of the prestigious journal Proceedings of the National Academy of Sciences of the United States of America (PNAS). *Although the top-line data for its phase 2a study in which pramlintide plus metreleptin caused an impressive 12.7% weight loss were released in November 2007, the article provides some further insights into the trial results. Weight loss continued to drop at the end of the study, suggesting that more significant weight loss may be achieved with longer treatment, and we believe that this combination will also be effective at weight maintenance because leptin is believed to be a long-term regulator of body weight. The article also presents preclinical data that mirrors the phase 2a data, and validates the theory that pramlintide sensitizes the brain to leptin. In rats (as in humans), leptin causes much more significant weight loss when it is used in combination with amylin, and the authors of the study show that in rats, amylin agonism increases leptin signaling in certain brain regions.*

Based on the trial design, the 12.7% weight loss achieved in this study could be viewed as a slightly inflated measure. The three main caveats are: 1) the weight loss is in comparison to study baseline, not a control arm, and thus it presumably includes a diet component; 2) 21% of patients were withdrawn in the pramlintide/diet lead-in period, such that the 12.7% weight loss was achieved in a somewhat selected pool of patients who may be better responders (see clinical data below); and 3) weight loss for pramlintide plus metreleptin was 10.8%, not 12.7%, using the more conservative intent-to-treat/LOCF analysis (see clinical data below). Nonetheless, the data are still certainly very impressive, in our view, and we remain highly optimistic about Amylin's peptide hormone approach to weight loss (the INTO program) because of its presumed safety profile.

- **Clinical data:** The present article provided details about Amylin's phase 2a proof of concept study for metreleptin plus amylin, for which top line data was first reported in November of 2007. As a reminder, this was a 24-week randomized, double-blind, active-drug-controlled study of 177 overweight or obese subjects with a BMI of 27-35. Mean weight loss for the metreleptin plus pramlintide arm was 12.7%, more than any currently marketed obesity agent. The study design was somewhat complex – there was a four-week, 40% caloric deficit diet plus pramlintide lead-in, in which 21% of subjects were withdrawn (9% due to insufficient weight loss, 3% for adverse events, and 10% for other reasons). Following this lead-in in which completers achieved an average of 4.3% weight loss, the remaining 139 subjects were randomized in a 2:2:1 ratio to pramlintide 360 μg plus metreleptin 5 mg, pramlintide 360 μg, or metreleptin 5 mg. Evaluable subjects achieved an average of 8.2% weight loss in the metreleptin arm, 8.4% weight loss in the pramlintide arm, and 12.7% weight loss in the pramlintide plus metreleptin arm (measured from study baseline, not randomization point). Using a more conservative measure of weight loss which measures the average weight loss of all subjects who completed the lead-in and were randomized but may or may not have completed the study (the so called intent-to-treat (ITT) or last observation carried forward (LOCF) measure of weight loss), subjects in the pramlintide plus metreleptin arm achieved an average of 10.8% weight loss, as compared to 7.5% for pramlintide monotherapy and 7.2% for metreleptin monotherapy. Of course, these results may still be somewhat enhanced from real-world results – as mentioned above, 21% of subjects were not included in this measure because they did not complete the lead-in; presumably, these patients were less compliant or had adverse reactions to pramlintide and would have brought down the average weight loss in all groups. Nonetheless, the study results are extremely impressive in our view, regardless of how they are analyzed. Safety and tolerability was very good overall – the most common side effects were injection site adverse events and nausea, which was "mostly mild to moderate and transient in nature."

- **The paper reports some preclinical data strongly supporting the notion that amylin and leptin work synergistically.** The authors show that amylin pretreatment in rats increased leptin signaling in certain regions in the brain, particularly the ventromedial hypothalamus and hindbrain area postrema. In rats, pramlintide and leptin cause approximately 15% weight loss and up to a 45% decrease in food intake – a synergistic effect. Moreover, the authors show that the synergy is specific to amylin and leptin (not other obesity peptides such as PYY or GLP-1), and that amylin's synergy with leptin is independent of its effect on food intake (amylin/pramlintide increase satiety). The synergistic action of leptin plus amylin was supported by the phase 2a human data as well – whereas metreleptin administration causes little or no weight loss in most obese subjects due to "leptin resistance," pretreatment with pramlintide prompted the metreleptin arm of the phase 2a study to demonstrate significant weight loss (see above). What is especially notable to us is the extent to which the metreleptin plus pramlintide human data mirror the preclinical data, suggesting that Amylin's rat model may be quite useful in predicting/assessing the efficacy of combination peptide hormone therapies in humans.

- **Although we rarely speculate with regards to such early-stage products, we believe that Amylin's INTO program may ultimately be game changing for the field of diabetes.** In spite of major advances in diabetes therapies over the past decade, therapies for obesity have remained relatively limited – options include lifestyle modification, which many patients struggle with; centrally-acting drugs associated with modest (~5% or less) weight loss and significant side effects; or effective but highly invasive surgical approaches. While bariatric surgery has been shown to be effective at preventing or reversing diabetes – a study by Dixon and colleagues that was published in the January 23, 2008 issue of *JAMA* found a 73% remission rate in recently diagnosed patients following gastric bypass surgery – bariatric surgery has had only a

small effect on the total diabetes prevalence because less than 1% of patients eligible for bariatric surgery (BMI over 40 or over 35 with an obesity-related complication) undergo a surgical procedure for obesity. Therefore, the rate of obesity continues to grow, driving the prevalence of diabetes. We believe that if Amylin's metreleptin plus pramlintide combination proves to be as effective, tolerable, and safe as the phase 2a data suggest (a big if, of course), it may offer the potential to significantly curb the progression from obesity to prediabetes and diabetes.

- **Is 12.7% weight loss the floor?** We'll have to wait for phase 2b or later, but the results from Amylin's phase 2a study suggest that even more significant weight loss may be attainable. Although the rate of weight loss for the pramlintide+metreleptin arm decreased towards the end of the study, a plateau was not reached. Perhaps more importantly, leptin is believed to be an essential hormone for body weight maintenance - therefore, we would expect that weight loss would be sustained. Given that the side effects of pramlintide+metreleptin in phase 2a were tolerable (see clinical data above), we wonder whether higher doses of leptin would possibly be used in future trials, perhaps causing greater weight loss. Amgen's clinical trial program included significantly higher doses of leptin, and these doses were found to be safe (although, of course, they were generally ineffective without the use of amylin).

- **Amylin's earlier stage INTO pipeline may provide even more effective peptide hormone mimetics and combination therapies.** Pramlintide was developed for the treatment of diabetes, not obesity, and therefore it is not optimized for weight loss. Amylin's second-generation amylin mimetic reduces weight even more effectively than pramlintide. At NAASO 2007, the company showed that its second-generation amylin mimetic reduced calorie intake by ~34%; by comparison, pramlintide reduces calorie intake by about 25%. We hope to learn more about this drug candidate at this year's ADA. Amylin is also working on hybrid GLP-1/amylin peptide mimetics, which could provide even more significant weight loss, and a poster for this hybrid will be presented at ADA. At last year's R&D Day, Amylin announced that its new focus with the second-generation amylin mimetic is the development of a sustained release formulation that may allow once-weekly subcutaneous dosing. There are certainly other obesity drugs in development that have shown double-digit weight loss, such as Orexigen's Contrave and Empatic, and Vivus's Qnexa, but we believe that the presumed safety of Amylin's peptide hormone approach could cause it to be used more broadly for the treatment of obesity, as a preventative strategy for diabetes and other aspects of the metabolic syndrome. Overall, we are enthusiastic about Amylin's approach to obesity therapy, and we believe that the best is yet to come.

—by Mark Yarchoan

9. Diabetes Comings and Goings

- **Dr. Alain Baron**, Senior Vice President of Research at Amylin, will be leaving as of May 30 to take on CEO responsibilities at an early-stage peptide company. He will consult for Amylin until his successor is named. At Amylin, Dr. Baron was primarily focused on early stage research, and managed the development of Amylin's impressive pipeline. We have been especially impressed with progress on leptin-based therapies and a program that we believe could ably address obesity (nothing else has worked due to a plethora of efficacy and tolerability and safety problems). While his departure is clearly a loss for Amylin, we are ultimately not so surprised as Dr. Baron strikes one as a more likely CEO than anything else.

- **Dr. Francis S. Collins**, director of the National Human Genome Research Institute (NHGRI) who has focused considerable research on the discovery of obesity and diabetes genes will be

leaving as of August 1 to explore writing projects and other professional opportunities. We look forward to following his work.

- **Dr. Jonathan Lord** was appointed as a Board Member of DexCom – see DexCom company news earlier in this newsletter.
- **Denny Ware,** who most recently served as CEO of Kinetic Concepts, was appointed to the Board of Directors of Pelikan Technologies. His experience at Boehringer Mannheim Corporation and Roche, prior to KC, will undoubtedly be useful to Pelikan.
- **Mr. William K. Heiden**, who is currently President and CEO of Elixir Pharmaceuticals, is joining the ConjuChem Board of Directors.
- **Susan P. Guerin** and **John E. Burrows** were appointed to the Board of Directors of Vyteris.

10. DCU Stock Chart and Final Thoughts

	29-May-08	29-Apr-08		2-Jan-08		29-May-07		IPO		Market Cap
SK	43.98	44.42	-1%	50.17	-12%	52.06	-16%	-	-	117.56B
NVO	65.63	65.48	0%	63.8	3%	51.82	27%	-	-	47.67B
AMLN	32.38	28.71	13%	36.95	-12%	45.12	-28%	14	131%	4.44B
SIRT	22.47	22.32	1%	13	73%	12.64	78%	10	125%	657.82M
PODD	16.98	19.06	-11%	23.42	-27%	15.27	11%	15	13%	467.56M
BIOD	15.78	13.63	16%	22.65	-30%	18.26	-14%	15	5%	373.31M
MNKD	3.05	2.23	37%	7.86	-61%	12.19	-75%	14	-78%	309.35M
OREX	8.90	11.41	-22%	13.94	-36%	16.83	-47%	12	-26%	305.35M
DXCM	7.96	7.81	2%	8.95	-11%	7.02	13%	12	-34%	234.63M
HDIX	8.00	7.75	3%	8.45	-5%	11.30	-29%	12	-33%	142.85M

Interesting time in diabetes stocks as always! Amylin rose 13% in the last month, presumably due to Icahn's purchase of so much stock! Some thought initially that he was going to do something on the order of his Yahoo positionings, but we think it's likely more about Icahn's group just advising him to buy on the value front alone. Amylin just had its annual meeting, so presumably if Icahn had something major in mind, he wouldn't be able to act on it anyway. We think Ginger Graham was right when positioning Amylin as a top 5 biopharmaceutical company and we would say it continues to head that direction despite the stock price. Mannkind stock was down then up on a percentage basis, increasing 37% in the last month; Biodel also rose nicely, up 16% on higher confidence about its super-fast-acting insulin trials.