DIABETESCLOSEUP

The Leading Source of Diabetes Business News

It's June. It Draws Many. It's ADA ...

May/June 2010 • No. 101

In all my years of following the diabetes industry, there has always been a major sense of excitement in the months (and certainly weeks) leading up to the start of the ADA conference. It may be the star-studded faculty in attendance, or the new data being presented, or the anticipation of the bustling exhibit floor. Whatever it is, the conference draws more than 25,000 people from around the world, passionately interested in treating, curing, and preventing diabetes. The anticipation, of course, begins long before ADA actually commences. Companies often delay reporting the complete results of closely-watched trials, so they can be presented at ADA. In the meantime, we are teased with "topline" results, which include just enough information for us to be enticed but not nearly enough to quench our thirst. Roche is a great example, with its once weekly GLP-1 agonist, taspoglutide; this compound has completed multiple phase 3 trials, and all we know is that the studies met their primary endpoints. Detailed results of five trials will be reported at ADA, for the first time. And while we kick and scream for detailed data as soon as the topline results are released, the delay simply increases the anticipation. Anticipation for data confirming the safety and efficacy of exciting novel therapies; for definitive answers to the question of tight glycemic control (in and out of the hospital); for trial results from large scale diabetes studies. This, for us, is exactly what makes ADA so special.

At Close Concerns, we count down the days until the start of this year's conference on June 25. We leaf through the day-at-a-glance schedule as soon it is released and sift through the endless list of abstracts the moment they become available. We organize our schedules around ADA to train the extra manpower that we bring in for the conference, so that our team can be in multiple places at one time (there are eight tracks, plus many poster sessions, countless symposia, and the football-sized exhibition floor). And yet, every year, ADA proves to be supremely worthwhile – whether it means getting a front row seat at the late-breaking clinical trial session or absorbing all the nuances, opinions, and questions about the latest drugs and devices. And we have no reason to believe that this year will be any different.

We have highlighted several fascinating sessions and symposia for ADA in this issue's Conference Preview section (page 47). Notably, Dr. Richard Bergenstal, the President, Medicine & Science of the ADA, will kick off the late-breaking clinical trial session by presenting results of the STAR 3 study, a one-year randomized controlled trial (funded by Medtronic) that compares the efficacy of sensor-augmented pump therapy to that of multiple daily injections (MDI). Though no long-term ACCORD-like clinical trials will be reported this year, we certainly look forward to fresh cuts of these data; for example, a late-breaker on the association between severe hypoglycemia and the risks of vascular events and death in the ADVANCE trial.

On the drug front, we're watching for key data on late-stage compounds as well as further detailed data on promising early-stage compounds. In late-stage development, SGLT2 inhibitor candidates will be high on our priority list, as they will almost certainly be the next major class of oral agents to enter the market. Obviously, the GLP-1 therapies will also be in full force, including Roche's taspoglutide, GSK's albiglutide (Syncria), Amylin/Lilly/Alkermes' Bydureon (EQW), and Novo Nordisk's Victoza (liraglutide). As for earlier-stage compounds, we hope to learn more about "next-generation" insulins (longer-acting basal insulins, short-acting bolus insulins, oral formulations, combinations with GLP-1)

that have the potential to transform insulin therapy. We also hope to see a slew of data on novel oral agents, such as IL-1 beta antibodies (XOMA's XOMA 052), glucokinase activators (Array BioPharma/Amgen's ARRY-403/AMG-151, Roche's Piragliatin, OSI Pharmaceutical's PSN010), selective PPAR gamma modulators (InteKrin's INT-131, Genfit's GFT505), PTP-1B inhibitors (ISIS's ISIS 113715), GPR119 agonists (OSI's PSN821), and various PPAR agonists (Roche's aleglitazar, Ono's ONO-5129, sanofi-aventis' AVE0897, Plexxikon's indeglitazar, Dara Biosciences' DB900).

On the device front, we hope to catch all studies and sessions related to the safety and efficacy of pump therapy (including novel forms of insulin delivery) and continuous glucose monitoring (CGM). Last year, we were impressed by the attention CGM received (as evidenced by the packed lecture halls during CGM talks) and this year we expect the presentations to be, if anything, more packed, as we watch CGM move into the mainstream. In addition, progress in the closed loop will be a topic of special interest – the ADA and JDRF are hosting what looks to be an exciting joint symposium on the Artificial Pancreas, co-chaired by Drs. Dick Insel and Richard Bergenstal, and featuring talks from Dr. Aaron Kowalski ("Are We Closer To Closing the Loop?"), Dr. Bill Tamborlane ("Landmark CGM Trials and Implications for Care"), Dr. Marilyn Ritholz ("Barriers to CGM Use"), and Dr. Roman Hovorka ("New Data on Overnight Closed Loop Studies"). Best yet – there will be Q&A for 45 minutes! Unheard of for ADA.

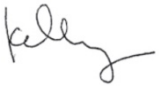
And what fun would ADA be without a little controversy? Former director of the FDA's Division of Metabolism and Endocrinology Products, Dr. David Orloff, will debate Dr. Steven Nissen, the Cleveland Clinic cardiologist who stirred the Avandia (GSK's rosiglitazone) controversy in 2007, on the need for a pre-approval cardiovascular risk requirement for diabetes drugs. On a related note, Dr. Sophia Zoungas will present fresh data on Avandia and the risk for cardiovascular-related outcomes in the BARI-2D study (initial results of this trial were announced at ADA 2009).

Finally, I would like to invite you to the Fourth Annual Close Concerns and TCOYD Diabetes Forum on Monday, June 28, at 6 pm at the Peabody Hotel. I will be lucky enough to moderate an unplugged panel of diabetes experts, who will have fascinating commentary on four days of intense ADA sessions. If you haven't signed up, please do so today at supporttcoyd.org, and save $25 from the onsite cost. All the funds go to TCOYD's amazing patient education, which is needed this year more than ever. Our esteemed panelists include:

- *The 2008 ADA Banting Lecturer Dr. Ralph DeFronzo of the University of Texas Health Science Center*
- *The ADA President-Elect Dr. Robert Henry of the VA and UCSD in San Diego*
- *Former ADA Physician of the Year Dr. Irl Hirsch of the University of Washington*
- *The ADA 2009 Educator of the Year Dr. Steve Edelman of the VA and UCSD in San Diego*
- *Obesity expert Dr. Francesco Rubino of the Weill Cornell Medical College*
- *Distinguished investigator Dr. Carol Wysham, Head of Endocrinology at the University of Washington*

The experts will present a fast-paced discussion, preceded by cocktails, hors d'oeuvres, music, and lights. This event will be hugely entertaining, and I cannot wait to discuss everything with these thought leaders and amazing clinicians. I hope to see you there ~ supporttcoyd.org.

Gratefully,



Kelly L. Close

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Sanofi-aventis – Announces plans to introduce BGM in India in 2011 – *page 22*
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- **Novo Nordisk** – Results of LEAD-6 extension study of liraglutide in *Diabetes Care*
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Videos

Below is our favorite video in diabetes this month:

- World Diabetes Day 2010 Official Launch Video
  http://www.youtube.com/watch?v=xA7QsnVXwM4&feature=youtu.be

Coming soon in DCU…

The major highlight of June is the American Diabetes Association (ADA) meeting. We have outlined the sessions we are looking forward to most in a Conference Preview of this issue; however, detailed abstracts will only become available in the next couple of weeks – if you are a Closer Look subscriber, you will receive a more detailed version later this month (contact alias.bekins@closeconcerns.com for any questions on this). We expect to hear trial results and fresh cuts of already reported data on a wide range of diabetes drugs and devices (as well as obesity drugs and devices). Right after ADA, we will stay in Orlando for the annual Children With Diabetes (CWD) Friends for Life conference. In July, we will be attending two powerhouse obesity meetings, the International Congress on Obesity (ICO) in Stockholm as well as the FDA advisory panel meeting for Vivus' Qnexa in Washington.

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1. Quotable Quotes in Diabetes

The "Pacman" approach

"It seems safe to assume, based on clinical and epidemiological evidence, that there are multiple types of obesity … I would estimate that there are several dozen or as many as a hundred different subtypes of obesity, each of which is likely to respond differently to different therapies.

Therefore, rather than trying to reduce the weight of the entire population, which is highly unlikely to succeed because of the heterogeneity of patients with obesity, I would seek a therapy that has a more profound effect (e.g., causes full remission of obesity) in a small percentage of the population. If you have a therapy that can eliminate or fully control obesity in even 1% of patients, then that population can be taken out of the "at risk" pool."

— Lee Kaplan, MD (Harvard Medical School, Boston, MA) discusses his "Pacman" approach to treating obesity in this issue's interview. One percent of any subgroup of obese patients, needless to say, is a very large number.

An Offer Insurers Can't Refuse

"I send the payors a letter saying that I believe [continuous glucose monitoring] is in the best interest of my patients' long-term survival and that I have notified them and their attorney that I am holding the insurer responsible for the long-term medical complications that result from inadequate glucose control. I get very few denials with that."

— Frank Schwartz, MD, FACE (University of Ohio, Athens) discusses how he addresses insurers who will not cover the costs of continuous glucose monitoring (CGM) at the 6th annual meeting of the Clinical Diabetes Technology society in San Antonio.

Challenging The Paradigm

"[Studies] suggest patients treated with stepwise metformin and sulfonylurea fail therapy, and their A1cs begin to climb – this is the ADA's treatment recommendation! That's an example of non-evidence based medicine."

— Ralph DeFronzo, MD (University of Texas, San Antonio) criticizes the American Diabetes Association (ADA) and European Association for the Study of Diabetes' (EASD) recommended treatment protocol at the 19th annual meeting of the American Association of Clinical Endocrinologists (AACE) in Boston.

2. diaTribe FingerSticks

— by Daniel A. Belkin

3. DCU Company Watch

- **Catabasis – Receives $39.6 million in Series A financing; advances type 2 oral drug targeting inflammatory pathways:** Cambridge, MA-based Catabasis secured $39.6 million in Series A Financing from SV Life Sciences, Clarus Ventures, MedImmune Ventures and Advanced Technology Ventures on April 1, 2010. So far, the company has received payments of just under $8 million with future funding dependent on reaching undisclosed development milestones. Catabasis co-founder and CEO Jill Milne, PhD and co-founder and CSO Mike Jirousek, PhD are both veterans of Sirtris Pharmaceuticals. Catabasis is developing a drug for type 2 diabetes code-named CAT1904, currently in pre-clinical trials. This compound is a conjugate of two generically available compounds: salicylate and an omega-3 fatty acid. Although salicylate has been described to lower glucose for over a century, it has not been commercially developed as a diabetes drug presumably because of its generic status. However, interest in developing salicylate for diabetes has grown in recent years as a result of work in this area by a number of researchers including Dr. Steven Shoelson's (Joslin Clinic, Boston, MA; co-founder of Catabasis Pharmaceuticals, Inc.). This research prompted the National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK) to fund a phase 2/3 clinical trial of salicylate for diabetes called the TINSAL-T2 study.

  By binding salicylate to an omega 3 fatty acid, Catabasis has turned generic salicylate into a patentable chemical moiety with potentially improved anti-inflammatory potency. Although the reported glucose lowering effects of salicylate are relatively modest (mean A1c reduction of 0.34% in the middle dose used in the TINSAL-T2 study, from a baseline of 7-9.5% A1c), the drug is believed to be very safe and tolerable. We look forward to seeing how its effect is enhanced by Catabasis' proprietary chemistry. Furthermore, because the drug is potently anti-inflammatory, we believe that the drug could have extraglycemic effects that could help prevent cardiovascular events via other mechanisms. While it will be years before we see long-term outcomes data, this funding is a big win for the company and underscores significant ongoing interest in the diabetes arena, even in a challenging venture capital environment.

- **J&J – Remains committed to innovation in diabetes in both pharmaceuticals and devices:** Alex Gorsky, Worldwide Chairman of the Medical Devices and Diagnostics Group of J&J, briefly referenced the 3.7% (1.0% operational) decline experienced in the Diabetes Care (devices) business in 2009, when revenue fell to $2.4 billion. He emphasized that J&J is confident it will return this industry to growth with new and innovative products in the coming years. He briefly mentioned that the OneTouch Verio would be the product to look out for next year as J&J launches what it is calling the next generation of accuracy and precision blood glucose monitoring system in markets around the world in 2010 (we believe this product will be accurate within ±15%, will not require coding, and will have memory functions to input meal and exercise flags). The company has released few details about this product, but as we understand it, Verio has been launched in the Netherlands with great success. We think it will serve J&J well in this environment to have an easy-to-use product, for which they can also tout accuracy.

  On the development front, the company's SGLT2 inhibitor, canagliflozin, was highlighted as an important late stage molecule with a significant opportunity to make a difference in the near future. The updated MD&D pipeline published in conjunction with the meeting suggests that there are two key filings planned for 2010: a PMA and CE Mark submission for an integrated continuous glucose monitor/insulin pump (presumably the DexCom/Animas integrated CGM/pump) and a submission to the FDA for a high accuracy blood glucose system version 2 (this follows on a 2009 filing of the first version of this system). Although there are certainly challenges on the SMBG front in particular, we were glad to hear about the company's commitment to diabetes. While there was no mention of obesity or the Bariatric Edge business at

the Investor Day, management did reference its growing wellness business at the meeting, noting that its recent acquisitions will be furthering its stake in the area; we are very interested in watching these businesses as presumably they will help J&J to play a role in curbing cardiovascular disease, obesity, and diabetes.

- **Orexigen – Further details on partnership preferences and reflections on the Qnexa panel:** CEO Mike Narachi led the 1Q10 financial update for Orexigen. The major highlight of the quarter was the submission of the Contrave NDA to the FDA. We look forward to the FDA's acceptance of the NDA and the announcement of a PDUFA date. During the call, Narachi emphasized that the company is seeking a pre-approval partnership. Although a global partner would be preferred, the "first priority" is partnering Contrave in the US, whereas Empatic and Contrave for ex-US markets are "potential options." In general, Orexigen's ideal partner would execute a successful launch of Contrave and lead the lifecycle management strategy. However, if the company is unable to secure an attractive partnership prior to approval, Orexigen is planning to launch with a targeted contract sales organization (CSO). Currently, the company is in discussions with "several CSOs." With regard to commercial readiness, Orexigen announced that it recently signed a manufacturing agreement with Patheon to produce a commercial supply of Contrave. On the financial front, Orexigen had cash, cash equivalents, and available-for-sale securities totaling $75.3 million as of March 31, 2010, compared to $92.2 million on December 31, 2009. Management continues to expect a cash burn rate of roughly $60 million for 2010; the current cash position is expected to fund operations at least until mid-2011. While the company previously stated that upfront partnership dollars would bolster the company's financial position, Narachi indicated that a large upfront payment is not the "primary objective" and suggested that Orexigen is currently favoring a backend-loaded deal.

  Senior VP of the global Contrave team, Preston Klassen, MD, MHS, discussed the company's presence at major upcoming medical meetings and the impact of the advisory committee meeting for Qnexa. Orexigen will have four poster presentations at ADA in late June and an impressive seven presentations at the International Congress on Obesity (ICO) in mid-July. Klassen was "pleased" that the FDA's Endocrinologic and Metabolic Drugs Advisory Committee has decided to host a panel for Qnexa and emphasized that while many issues will be drug-specific, a favorable outcome would be positive for the field. While he cautioned against broadly generalizing the results to other obesity products, he did note that the company will be paying close attention to the meeting, especially regarding the use of anticonvulsants in treating obesity (as a reminder, Empatic includes an anticonvulsant, zonisamide). Any information on anticonvulsants may provide insight into the phase 3 program as well as help potential partners value Empatic. Orexigen also hopes to gain additional perspective on general marketing and postmarketing requirements for obesity products.

- **Arena – Preparing for an expected advisory committee meeting:** CEO Jack Lief led the 1Q10 financial results for Arena. The company is currently focused on preparing for an expected advisory committee meeting, engaging in discussions with potential partners, and gearing for a timely launch. According to the FDA guidance, Lief indicated that the agency tends to notify sponsors 55 business days prior to an advisory committee meeting. However, we note that the advisory panel for Vivus' Qnexa was scheduled nearly three and half months in advance (over a 100 days prior to the meeting). As a reminder, the initial PDUFA date for Qnexa is set for October 22, 2010. While Arena has not received such notification of whether an advisory committee meeting will be required for the review of lorcaserin, management pointed to a placeholder for an Endocrinologic and Metabolic Drugs Advisory Committee (EMDAC) meeting September 15-16. On the clinical development front, BLOOM-DM is on track to complete treatment of the last patient "around" the end of June 2010, and we expect to hear results from this trial later this year.

As a reminder, data from BLOOM-DM will be included in a supplement to the lorcaserin NDA (intended to be filed post-approval). The manuscript covering the BLOOM results is currently under review and Arena is preparing to submit the BLOSSOM data for publication soon. Management mentioned that the manuscript includes an extensive analysis of glycemic control, including measures of glucose, insulin, insulin resistance (HOMA-IR), A1c, the use of antidiabetic drugs, and the diagnosis of diabetes. We look forward to presentations on post hoc analyses of the combined dataset for lorcaserin at ADA and CBI's 6th Annual Obesity and Diabetes Drug Development Summit. On the financial front, Arena had cash and cash equivalents of $108 million as of March 31, 2010, compared to $115 million on December 31, 2009 and $144 million on September 30, 2009. The next debt payment is $20 million to Deerfield in mid-2011.

During the Q&A, Lief emphasized that he prefers and expects a partnership to be finalized prior to approval. We were slightly surprised that he characterized the advisory panel for Qnexa as "irrelevant" with respect to securing a partner, especially given the uncertainty surrounding the FDA's view on obesity drugs. That said, management did allow for the possibility of a launch by Arena alone and said an internal sales force of about 100 could target roughly 7,500 physicians responsible for about half of all obesity drug prescriptions. Management also mentioned in Q&A that the 120-day safety update to the FDA included data from the BLOOM-DM study relating to frequent adverse events, adverse events that led to study withdrawal, and serious adverse events. Management said it is planning to provide data on cardiovascular outcomes at "upcoming meetings." Management clarified that external adjudication was not performed for cardiovascular events (Vivus has previously mentioned that data on CVD outcomes may not be available for the advisory panel due to the external adjudication process). We continue to believe the success of lorcaserin is largely dependent on how well it works in combination with other drugs.

- **XOMA – Announces the initiation of a Phase 2b trial for XOMA 052 in 1Q10 update:** In a call led by CEO Steve Engle, XOMA announced 1Q10 results. Of note, the six-month phase 2b trial of anti-IL-1 beta antibody XOMA 052 has been initiated. As a reminder, the phase 2b trial will evaluate the efficacy and safety of four doses of XOMA 052 in 325 type 2 diabetes patients on stable metformin therapy with topline results expected in 1Q11. In the Q&A, management expressed confidence that the phase 2 program would better reflect the drug's efficacy than phase 1 trials (phase 1 studies demonstrated a slight but significant 0.6% A1c reduction), given the longer duration of study, tighter control of background medication, and wider variety of dosing regimens. We certainly feel more evidence on the longer-term glycemic effects and side effect profile of XOMA 052 will be necessary to gauge the drug's potential. We expect any early signs of cardiovascular benefit in phase 2 trials to strengthen partnership discussions (though we believe it will be challenging to show convincing results from a 26-week trial regardless of actual results).

  While management did not clarify whether potential partners were awaiting results from the phase 2b trial or solely the phase 2a trial (three-month interim results are currently expected in 4Q10), given the company previously suggested the phase 2b trial would be on hold until a partnership was solidified, we suspect discussions will continue until after topline results from the trial are announced in 1Q11. In the Q&A, management suggested XOMA's recently secured patents for XOMA 052 were bolstering interest from potential partners, though they could not comment on the coverage offered by the patents. Unfortunately, progress in the JDRF-funded phase 2 trial for the treatment of type 1 diabetes remains slow – due to unpredictable enrollment rates, management suggested initial data would not be available until sometime in 2011. We are uncertain whether this reflects the number of patients that meet enrollment criteria (patients must have an A1c <7% and must have some healthy beta cells) or whether some patients may be concerned about safety. Only 24 participants are needed and they are required to take only a monthly injection for six months.

On the financial front, XOMA held $28.4 million in cash, cash equivalents, and short-term investments as of March 31, 2010, compared with $23.9 million at year-end 2009; management suggested this would allow the company to continue operations through the next 12 months. No update was given on the company's proceedings with the NASDAQ qualifications panel, though management plans to announce the panel's decision as soon as it becomes available.

- **Insulet – Revenue grows to $21 million in 1Q10, with gross margins of 40%; next-gen pod submission expectation refined to 3Q10:** CEO Duane DeSisto led the 1Q10 update for Insulet. The company continued to grow strongly in 1Q10, reporting $20.8 million in revenue, up 67% from $12.5 million in 1Q09 and $20.2 million in 4Q09. As a reminder, the first quarter tends to be the slowest quarter, as new patient additions from late 2009 defer training until the first quarter and reorder in the second quarter. Despite the relatively slow start, referrals were up more than 20% in 1Q10 as compared to 1Q09, which is a quite positive sign in our view given that the smaller pod and the pod/CGM integrated product will also drive demand when they are both available (possibly late 2011, but likely early to mid 2012). The company expects 2Q10 revenue of $22-23 million. On the gross margin front, Insulet achieved a record quarter in 1Q10 with gross margins of 40%, up from 36% in 4Q09 and from 16% in 1Q09. The company is making progress toward hitting its 50% gross margin target by the end of 2010 – we had seen that as a very ambitious goal and still would be very impressed if they achieved it. Management looks for a 60% gross margin "around 2012", another ambitious goal even given the impressive progress to date. Operating loss for the first quarter of 2010 was $10.7 million, nearly 40% less than the $17.5 million operating loss in 1Q09 and particularly impressive given that 12 new clinical specialists were hired recently. DeSisto said in Q&A that the company targets mid-2011 to get to cash breakeven. Insulet held cash and cash equivalents of $118.3 million at the end of 1Q10, compared to $128.0 million on December 31, 2009.

  On the development front, submission of the next-generation OmniPod is now planned for 3Q10 – refined from previous estimates of submission in mid-2010 (technically, a July or August submission would be both "mid-year" as well as "3Q"). We expect a three to six month review period, so while it is possible approval could come in late 2010, 2011 is more likely. We will be looking forward to the FDA's scheduled infusion pump workshop on May 25-26 to better assess how the current premarket and postmarket regulatory processes may change in the near future. On the international front, Insulet/Ypsomed still plan to launch the OmniPod in the UK and Germany in 2Q10, with launch in additional markets through 2H10 and into 1H11. Finally, as noted in DexCom's 1Q10 update, management highlighted that DexCom filed a PMA supplement for the first-gen CGM-integrated OmniPod in 1Q10, with an FDA response expected within a 180-day period "give or take a few months." This is certainly a major positive in our view. According to our dQ&A data, access to CGM within the same device as the pump is considered a major benefit by many pumpers, as is a smaller pump (or pod)– the potential for both in a system will be considered major improvements by many (for more information on dQ&A market research, please contact: richard.wood@d-qa.com).

- **Amylin/Lilly/Alkermes – Bydureon receives new PDUFA date of October 22, 2010:** Amylin/Lilly/Alkermes announced that the FDA has classified the Bydureon complete response as a Class 2 resubmission and has set a new PDUFA date for the drug of October 22, 2010. As a reminder, the companies received a full response letter from the FDA on March 12, 2010. The agency's requests in the letter were related to the finalization of the product label, Risk Evaluation and Mitigation Strategy (REMS), and clarification of the existing manufacturing process, but it did not request any new pre- clinical or clinical data or re-analysis of any existing data. Amylin submitted its complete response letter to the FDA in April, 2010. At the time, it was unclear whether Bydureon would be a Class 1 or Class 2 submission, the latter being a lengthier and more

involved process. The Class 2 designation is disappointing from both a patient and commercial perspective, as the drug will now be delayed for six months, as opposed to the 60 days entailed in a Class 1 response.

During the Q&A of the March 15, 2010 conference call concerning the FDA's response letter, we learned that the FDA had proposed a label for Bydureon, but management did not disclose the content of that label and noted they would be addressing the proposed label in their response to the FDA. As we have mentioned before, while we expect the path for the REMS program and manufacturing process clarification to be relatively straightforward, more controversy could take place over the product label for Bydureon, and we suspect that the longer review entailed in a Class 2 designation could stem from this issue. The FDA's decision to classify the resubmission as Class 2 may speak to some of the issues raised in the complete response letter by the companies. During the Q&A of the March 15, 2010 call, Amylin CEO Dan Bradbury mentioned that although REMS negotiations can be a gray area for resubmission timelines, he did not expect this to be a major issue between the agency and the partnership based on what was in the FDA's response letter. How Bydureon will be differentiated from Novo Nordisk's Victoza label is an important question—especially now that Victoza will have close to a full year on the market before Bydureon could potentially be launched. The fact that labeling issues were raised in the FDA's response letter makes us optimistic in that the drug is close to approval, even though this lengthier assessment period is a setback.

- **Biodel — Prepares for launch of VIAject and pipeline development:** New president and CEO Dr. Errol De Souza led the call for Biodel's F2Q10, shedding light on the company's path ahead as a focused diabetes company. Biodel reported a net loss of $10.4 million in F2Q10, an improvement of 10.3% from a loss of $11.6 million in the same period one year ago. R&D expenditures were $7.0 million in the quarter, down 16.7% from $8.4 million in F2Q09. At the end of F2Q10, cash and cash equivalents totaled $32.7 million, down 40.1% from $54.6 million in F2Q09.

  The focus of the call was not only on VIAject, for which an NDA was submitted to the FDA in December of 2009 with an expected PDUFA date of October 30, 2010, but also on the strong pipeline of compounds currently in earlier stages of development including basal insulins, second generation ultra-rapid acting insulins, VIAtab, and stabilized glucagon. Notably, during Q&A, management mentioned it may have a next generation basal insulin (characterized as "an improved glargine") available in 2014. Although details are still elusive on the partnership front, during Q&A, management noted that potential partners have been expressing interest beyond VIAject and looking to innovations in the pipeline with enthusiasm. For this reason, the company has increased investment in these areas of product development (it probably also explains Dr. Sol Steiner's recent move from CEO to Chief Scientific Officer). Biodel is undertaking efforts to prepare for the launch of VIAject while awaiting the FDA's decision; both scenarios in which the launch would occur with a partner and without a partner are being discussed and addressed. In addition to the usual elements of the NDA process, the company will continue to present new analysis from the phase 3 trial of VIAject in type 1 and type 2 patients as well as data from new studies comparing VIAject to insulin lispro (Lilly's Humalog) at the upcoming ADA meeting. During the Q&A, management also discussed several questions related to VIAject pump trials in type 1 patients, noting that the two ongoing small pilot trials will be completed by the end of this year and would influence the design of a large definitive pump trial to be initiated thereafter. Management also noted the company is looking to initiate more studies to "maximize the potential" of VIAject.

- **ISIS Pharmaceuticals – Management highlights plans for an "exciting ADA":** In a call led by CEO Stanley Crooke, ISIS Pharmaceuticals announced 1Q10 results. While the call primarily focused on the company's recent alliance with GSK to develop infectious disease treatments, Crooke highlighted developments from ISIS' metabolic pipeline planned for presentation at this year's ADA in June. In particular, he noted that phase 1 trial results with ISIS-GCGRRx (targets the glucagon receptor) and full phase 2 trial results for ISIS1131715 were scheduled for oral presentation and that initial data from the company's fledgling obesity program (likely animal data with ISIS' FGFR4 inhibitor) were scheduled for poster presentation. As a reminder, J&J's Ortho-McNeil recently returned the rights of ISIS-GCGRRx to ISIS – we will be listening carefully to ISIS' presentation on the candidate to gauge whether Ortho-McNeil was disappointed with the results and where ISIS could make improvements for future candidates in the program. While the potential partnership of ISIS1131715 is likely on hold until the longer 26-week trial can be completed, we will be particularly interested to hear any data on the patient experience – surely a shot taken once a week or once a month with a favorable side effect profile should appeal to patients. In the Q&A, Crooke also noted additional measures being taken with ISIS' latest stage candidate mipomersen, which targets apolipoprotein B-100. Theoretically, targeting apolipoprotein B-100 would inhibit the absorption of dietary triglycerides, leading to a reduction in serum triglycerides (an important marker of cardiovascular risk).

  On the financial front, ISIS ended 1Q10 with $519.1 million in cash, cash equivalents and short-term investments, compared to $574.3 million at the end of 2009; management provided guidance suggesting the company would end 2010 with roughly $425 million. Given a $35 million upfront payment from GSK is on the way, we feel ISIS is well positioned to bolster research efforts in the upcoming quarters, particularly for ISIS1131715 (initiation of the much-needed 26-week phase 2 trial is currently planned for sometime in 1Q11 or 2Q11) and the company's SGLT2 inhibitor ISIS-SGLT2Rx (initiation of phase 2 trials is planned for sometime in 2010). Interestingly, on the prospects of the company's SGLT2 program, in the Q&A, Crooke suggested ISIS-SGLT2Rx could show improved efficacy (due to the drug's ability to knockout 90%-95% of SGLT2, versus roughly 50% inhibition with oral options) and gastrointestinal safety (due to increased specificity for SGLT2 versus oral options) over the potentially more patient-friendly oral candidates in the space – we will be monitoring phase 3 trials with oral candidates in development closely for early signs of potential differentiation.

- **DexCom – Product revenue and gross margin sustained in 1Q10; PMA filed for CGM/OmniPod combination:** DexCom announced very strong 1Q10 results in a call led by CEO Terry Gregg. Product revenue in 1Q10 was $6.8 million, up a strong 152% from $2.7 million in 1Q09 and up 3% from $6.6 million in 4Q09 – as a reminder, this follows an impressive 4Q09 (always the strongest quarter seasonally), in which product revenue rose 169%. As forecast in DexCom's 4Q09 call, management attributed the slowdown in sequential growth to seasonal factors, such as the resetting of annual insurance deductibles and inadequately funded employer flexible spending accounts. Gregg estimated that over 90% of DexCom users have some insurance coverage and that coverage was becoming slightly easier to obtain. Interestingly, Gregg noted in the Q&A that some softening was expected as the CGM category matured: compared to "early adopters" of technology that boosted sales in early quarters, he suggested new users are now much more price-sensitive in terms of co-pay, regardless of prior authorization from payors. However, he affirmed that this effect began to diminish later in the quarter and that sales carried on strong into 2Q10. We suspect DexCom will maintain a stable sequential growth rate as awareness of CGM increases and the reimbursement environment improves. Currently, only a small percentage of intensively managed patients use CGM regularly so there is still significant upside. Total revenue in 1Q10 was $9.5 million, up 83% from 1Q09 though down 9% from 4Q09

(however, as a reminder, total revenue in 4Q09 was bolstered by a one-time $3.8 million development grant). Revenue in 1Q10 represents 2,600 systems sold, down 9% sequentially – representative of the seasonal slowdown noted above. Sensor revenue increased 4% sequentially in 1Q10, maintained from the 50% increase observed in 4Q09. Clearly, as emphasized in the Q&A, given that new system units sales are down, patients must be trending towards more frequent sensor utilization, likely somewhat driven by continued education about benefits of continuous use. We recently got back dQ&A data (our patient panel with over 300 CGM users) that indicated that DexCom users do use DexCom systems "full-time" (i.e., 24/7) more than do the users on competitive systems (for more details on this, contact: richard.wood@d-qa.com). Also of note, product gross margin continued strong at $1.6 million in 1Q10, or 24% of sales, up from $1.15 million in 4Q09 or 17% of sales. This is the third quarter that the company has posted a positive gross margin; management attributed the rise to additional manufacturing overhead absorption, reflective of an increase in inventory to accommodate for current and future increases in sales.

On the R&D front, and on an exciting note, DexCom recently filed a PMA supplement with the FDA for its first-generation integrated system with Insulet's OmniPod. The company hopes that the FDA will review the PMA supplement within a typical 180-day period "give or take a few months." As a reminder, this combination product will include the third-generation sensor and management noted in the Q&A that switching to the fourth generation sensor should be a "simple path" and wouldn't require the patient to obtain a new handheld device. For the Animas pump/CGM combination, DexCom remains on track to file a PMA supplement later this year. In addition, the company completed a pivotal trial for its fourth- generation sensor and expects to file a PMA supplement with the FDA before the end of 2Q10; we look forward to further details on this sensor, which will be announced in the 2Q10 financial update, but as we understand from prior announcements, there will be a range of improvements with regard to accuracy and ease of use. DexCom also completed a trial last summer required to support an FDA submission of the first- generation blood-based glucose monitoring system for the critical care environment, pending final analysis of the data. Even though there was a limited launch of the first-generation device in Europe, Gregg indicated that the second-generation monitor would be launched globally mid-to-late next year following the approval of a supplemental submission.

When asked about ADA, Gregg pointed out that Medtronic's Star 3 trial is going to be presented, which he said favored pumps and CGM, although regrettably, he said, that the trial only compared pumps and CGM to MDI and SMBG and did not compare pumps and CGM to MDI and CGM. As such, he said it was a very flawed trial and that onlookers would just have to be careful about reading the outcomes of the trial and understanding them.

- **GI Dynamics – Announces topline data from two studies evaluating the EndoBarrier:** GI Dynamics just announced topline results from two studies of the second-generation EndoBarrier Gastrointestinal Liner at the Digestive Disease Week (DDW) in New Orleans. As a reminder, the EndoBarrier is a 60 cm fluropolymer liner inserted into the intestine to create a physical barrier between ingested food and the intestinal wall. These two prospective single-arm studies were conducted in Brazil and Chile and assessed the efficacy and safety of the EndoBarrier in 61 patients. One study recruited 22 obese patients with type 2 diabetes. At baseline, these individuals were in poor metabolic shape, with a mean baseline BMI of 44.9 kg/m2 (±1.6 kg/m2) and a mean baseline A1c of 8.9% (±0.4%). Monthly follow-up visits were conducted to assess weight loss, A1c, and any safety issues. After 24 weeks of treatment with the EndoBarrier, patients (n=16) experienced an average reduction in A1c of 1.5% (±0.4%) and 58% of patients (7/12) achieved A1c levels of ≤7%. The second study evaluated the EndoBarrier in 39 obese patients with a mean baseline BMI of 43.8 kg/m2 (±0.9 kg/m2). The mean reduction in total body weight after 24 weeks (n=48) was 15 kg (±1.1 kg), or 13.1% (±0.9%); patients from the

diabetes study were also included in this analysis (weight loss results from separate studies were not reported). Overall, there was one migration of the EndoBarrier, representing a significant improvement over the first-generation EndoBarrier, and the device was removed in eight individuals prior to the completion of the study due to "device-related adverse events." No further details were provided on adverse events in this study.

The company is currently preparing to commercialize the EndoBarrier in Europe, where it is approved for six months of continuous use. We look forward to further 12-month data on the EndoBarrier, which will be presented at the International Federation for the Surgery of Obesity (IFSO) in early September in Los Angeles. As a reminder, GI Dynamics recently reported topline data from a 12-month trial of the second-generation EndoBarrier. While these data represented only six patients treated with the EndoBarrier, the patients experienced a mean A1c reduction of 2.5% (±0.6%) from an even higher mean baseline A1c of 9.3% (±0.8%), suggesting that a 12-month implantation of the EndoBarrier has a progressively positive glycemic benefit compared to a six-month implantation of the device.

- **Merck – Januvia franchise posts strong growth of 32%; Januvia approved for use with insulin:** CEO Dick Clark led the 1Q10 financial results for Merck. The Januvia franchise (consisting of Januvia and Janumet) achieved global sales of $712 million in 1Q10, a 32% jump from $529 million in 1Q09. Worldwide sales of Januvia came in at $511 million in 1Q10, up 24% from $411 million in 1Q09, and worldwide sales of Janumet reached $201 million in 1Q10, a 56% gain from $128 million in 1Q09. Management attributed the sequential decline in sales to inventory buildup in 4Q09, which is being "adjusted downward" in 2Q10 – this makes sense to us given the 23% increase from 3Q09 to 4Q09 (although at the time, management did not mention inventory buildup and it hadn't occurred to us).

  Merck continues to invest in promotions for Januvia to maintain its (massive) leadership position in the DPP-4 inhibitor market. Despite the recent introduction of Onglyza (BMS/AZ's saxagliptin) and continued relentless generic competition (from metformin and sulfonylureas), Januvia continues to grow strongly in the US and international markets. Management emphasized the "differentiated label" for Januvia, specifically citing the approved use of Januvia in combination with insulin (with or without metformin). As we understand it, this indication was approved as part of a recent revision to Januvia's label in late February 2010. Merck continues to highlight the strong value proposition for Januvia compared to sulfonylureas; as a reminder, in the 4Q09 financial update, management outlined a strategy to grow the franchise by taking share from sulfonylureas as a second- line therapy for type 2 diabetes patients. Management also suggested that the launch of Januvia in Japan is progressing well and notably, Merck expects this market to be a major growth driver for the Januvia franchise. In the Q&A, management reiterated its focus on competing with established generics and did not view GLP-1 therapies as a threat to the DPP-4 inhibitor market, specifically noting that Victoza's growth has not come "at the expense of Januvia."

- **GSK — Avandia sales continue to tumble and take an especially hard hit in the US; Alli sales picking up:** In the 1Q10 call led by CEO Andrew Witty, GSK announced that Avandia Franchise sales fell to £169 million ($263.6 million), a 14% decline (6% operationally) compared to 1Q09 earnings of £197 million ($281.7 million). This reflects declines in domestic Avandia Franchise sales from £112 million ($160.2 million) in 1Q09, to £89 million ($138.8 million) in 1Q10, a reported loss of 20.5% or 13.3% operationally. Internationally, Avandia Franchise revenue fell to £80 million ($124.8 million) in 1Q10, down 5.9% on a reported basis from £85 million ($121.6) in 1Q09. Sequentially, worldwide Avandia Franchise sales declined 11.5%, reflecting sequential declines in US sales of 18.3% and sequential international sales declines of 2.4%. Until

this quarter, the company had broken out Avandia and Avandamet sales, which together typically amount to about 95% of total Avandia Franchise sales with Avandaryl (rosiglitazone plus glimepiride) making up the third component, but GSK appears to have abandoned this practice, reporting Avandia Product sales on a single line on the balance sheet. Avandia typically pulls in the majority of the revenue by a fairly slim margin (approximately 60% of the revenue is contributed by Avandia per quarter). Considering the tumbling of year-over-year sales and substantial sequential drop in the US, it seems safe to assume that the recent flare-up of renewed controversy over Avandia (rosiglitazone), fanned by the US Senate Finance Committee's Report accusing both GSK and the FDA of inappropriately responding to the signals of cardiovascular risk associated with the drug in Dr. Steve Nissen's (Cleveland Clinic) meta-analysis, has continued to impact sales of the drug in the US. It is no secret that some stakeholders are pushing for the drug to be removed from the market, but CEO Andrew Witty seemed confident during Q&A that Avandia is a very different situation than the Vioxx scandal experienced by Merck several years ago. Interestingly, Avandia occupied very little of GSK's conference call, aside from the question posed during Q&A about the likelihood of the drug being removed from the market and a brief statement in the press release suggesting the company remains committed to transparency and patient safety.

Worldwide Alli sales showed strong growth in 1Q10 with sales rising to £63 million ($98.3 million) worldwide, a 58% increase (72% operationally) over sales of £40 million ($57.2 million) in 1Q09. In 1Q10 sales of Alli in the US increased year-over-year to 27.3% to £28 million ($43.7 million). International sales of Alli in 1Q10 increased a substantial 94.4%, growing to £35 million ($54.6) from £18 million ($25.7million) in 1Q09, driven by strong uptake in Europe (the drug was introduced there last March).

- **Becton Dickinson — Strong growth in Diabetes Care Franchise of 11.6%:** In a call led by President Vince Forlenza, Becton Dickinson's Diabetes Care franchise reported strong F2Q10 results. Diabetes Care sales totaled $188 million in F2Q10, up 11.6% (10.2% operationally) when compared to the same quarter last year. Sales in the US rose to $92.5 million, up 11.2%, and international sales grew to $95.5 million—an increase of 12.1% (9.3% operationally). Sequentially, total Diabetes Care sales fell 6.7%, reflecting a sequential decrease of 4.2% in the US and 9.0% in international markets. Management noted that the strong first quarter performance was driven by sales of pen-needle products, especially in emerging markets, and revenue from a non-product co-marketing agreement, the details of which have not been disclosed (while this could be the JDRF partnership to improve insulin pump therapy and explore the development and commercialization of microneedles, we suspect it is something else – there is clearly a lot of outside interest in BD's diabetes franchise given the company's expertise in insulin delivery. Diabetes Care is part of the Medical business segment at BD, which grew 9.7% (7.8% operationally) in the quarter. Management cited the Diabetes Care franchise as one of the key drivers for growth in the Medical business segment in F2Q10. Management has previously forecasted global revenue of 8-9% for Diabetes Care in 2010 and these forecasts were not revised during this quarter's call.

  Although it is challenging to get a handle on BD's Diabetes Care product pipeline (as it is not explicitly broken out or discussed during the earnings calls), during Q&A management mentioned the product referred to as the "Nano" was recently approved and that we can expect more updates on other new products in late F1Q11 or early F2Q11 (this product is advertised as the "smallest pen needle ever," expected to be launched in June: http://www.bd.com/us/diabetes/page.aspx?cat=7002&id=32521). In addition, BD has benefitted from significant headwind in pen needle sales for the last several quarters due to a successful partnership (the partner has not been disclosed); however, the forecasted favorability from this

partnership is expected to decline by the end of 2010, but will be ultimately offset by new product launches.

- **Vivus – Preparations underway for upcoming advisory panel:** CEO Leland Wilson led the 1Q10 update for Vivus. As a reminder, the FDA recently scheduled a tentative advisory committee review for Qnexa on July 15, 2010 (in Q&A, Wilson clarified that "tentative" is standard FDA language – we were surprised that the meeting was scheduled to take place during the International Congress on Obesity and are hoping it might be rescheduled though we understand this is unlikely). The company is focusing on preparing a briefing document as well as several slides to address any potential questions from the panel. The REMS program for Qnexa will be presented at the meeting, and management hinted that it will be "nothing unusual or different" than what is currently available for topiramate, with respect to the medication guide and communication guide to patients and providers. The two-year safety and efficacy data from the EQUIP and CONQUER studies will be released in the second half of this year; if available, management hopes to draft a topline report of these data for the advisory panel meeting. This data will be an important milestone and we assume that reassuring results would serve the company well. Wilson reiterated his confidence in the psychiatric side effect profile of Qnexa; interestingly, he noted that up to 30% of patients enrolled in clinical trials had "some psychiatric history" and a "high-teen" percentage of patients were on antidepressants. We view this as a positive that such patients weren't excluded from the trial.

  On the financial front, Vivus had cash, cash equivalents, and available-for-sale securities of $194.9 million as of March 31, 2010, a 5.8% decline from $207 million on December 31, 2009. The company continues to guide for a cash burn rate of approximately $95 million for 2010. President Peter Tam highlighted Vivus' presence at major upcoming medical meetings in the US and Europe, including the American Society of Hypertension, EUROprevent, World Congress on Controversies to Consensus in Diabetes, Obesity, and Hypertension (CODHy), SLEEP 2010, Endocrine Society (ENDO), ADA, and International Congress on Obesity. In other company news, management said that the FDA hasn't yet inspected the Qnexa plant. Notably, Vivus recently appointed Michael Miller to serve as a Senior Vice President and Chief Commercial Officer. Most recently, Miller was the Vice President at the BioOncology Business Unit at Genentech. He also worked at Vivus some years back on the Muse launch, so he is well-known to management and highly regarded. We assume the Genentech experience will be important and will serve the company well. In addition, two board of directors recently announced they will not be standing for re-election, Graham Strachan and co-founder Virgil Place; Wilson emphasized that these decisions were purely personal and not related to Vivus.

  During the Q&A session, Wilson noted that a positive panel outcome could trigger a partnership decision; however, he anticipates that a potential partner will likely expect an FDA approval "before the ink dries." Finally, Vivus continues to work with the FDA on a phase 3 development program for Qnexa for the treatment of sleep apnea and clarified that it will work with the FDA to design trials and establish clinical endpoints under a special protocol assessment (SPA).

- **Allergan – Sales of the LAP-BAND remained relatively flat; potential DME indication for Ozurdex:** CEO David Pyott led the 1Q10 financial update for Allergan. The obesity intervention business (consisting of the LAP-BAND, the EasyBand, and the Orbera intragastric balloon system) increased slightly on a reported basis, bringing in sales of $61.2 million in 1Q10, a 2.3% increase from $59.8 million in 1Q09. In local currencies, the obesity business declined 2.2% from 1Q09. Small declines in the US were offset by "reasonable" growth in ex-US markets, especially Canada and the UK. While the self-pay segment has been declining for the past two years, management suggested that it has now "bottomed out." We assume that the

economy and high unemployment rate continue to impact the self-pay segment, given that the out-of-pocket cost for the LAP-BAND is over $14,000. However, Allergan has maintained 75% market share in the gastric band market, giving up just 2% share loss to Ethicon's REALIZE gastric band over the past year, according to management. Sales of Allergan's Orbera intragastric balloon grew strongly, although from a small base, in Europe, Australia, and parts of Latin America (numbers for individual products within the obesity intervention business are not separately reported). As a reminder, the Orbera intragastric balloon is endoscopically inserted (non-surgically) for six-months to reduce stomach capacity and promote satiety; it is approved in over 60 countries (not including the US) for treatment in overweight and obese adults. Management estimated that the worldwide bariatric surgery market for gastric bands and balloons is roughly $360 million, declining at rate of 7%; Allergan currently has an overall market share of approximately 59% in the band and balloon segments.

During Q&A, management briefly mentioned exploring a diabetic macular edema (DME) indication for Allergan's Ozurdex, an FDA approved therapy for the treatment of macular edema following branch retinal vein occlusion (BRVO) or central retinal vein occlusion (CRVO). A small trial has been conducted in DME patients undergoing vitrectomy (removal of some or all of the vitreous humor from the eye) and the results were positive. However, management suggested that an indication for DME will require a three-year study. Nevertheless, we look forward to more updates on Ozurdex for the treatment of DME.

- **MannKind – Preparing for FDA meeting; plans to file amended NDA within weeks of meeting:** CEO Alfred Mann led the 1Q10 financial update for MannKind. The company is preparing for its response to the Complete Response Letter by compiling a briefing book for its follow-up meeting with the agency, scheduled in early June. Chief Scientific Officer Peter Richardson outlined plans to submit the response (anticipated to be a class 2b submission) to the FDA "within weeks" of this meeting. The briefing book will contain additional data, including results from a new study, MKC-117, comparing Afrezza to Humalog (Eli Lilly's insulin lispro), as well as a bioequivalence study comparing the second-generation Dreamboat device to the MedTone (model C) device used in long-term clinical trials. The MKC-117 study met the primary endpoint of non-inferiority regarding the change in A1c between the Afrezza arm and the Humalog arm. In addition, according to management, the bioequivalence study has confirmed that the pharmacokinetic profiles of the two devices are "indistinguishable." Management also confirmed that the Dreamboat will meet the FDA's requirements of labeling the product in insulin equivalent doses. Importantly, instead of filing a supplemental NDA following the approval of Afrezza with the first-generation MedTone device, the company has revised its regulatory strategy and now plans to file an amended NDA for the second-generation device as part of its response to the complete response letter.

  MannKind continues to engage in partnership discussions with "several pharma companies" (some of which have been included in preparations for the FDA meeting) but does not expect to engage in detailed negotiations until at least after the meeting with the agency. Management remains open to "strategic options that could extend [their] cash position further into next year." On the financial front, the MannKind is instituting multiple measures to cut the cash burn rate, defer expenses, and strengthen the overall cash position of the company. For example, clinical studies that are not critical for the regulatory submission of Afrezza have been postponed. Cash, cash equivalents and marketable securities totaled $31.5 million as of March 31, 2010 and the cash burn rate for 1Q10 was $45 million. The remaining available credit from Al Mann' amounted to $145 million as of March 31.

- **Bayer — Solid Contour sales in 1Q10 are offset by flat Breeze growth:** In a call led by CEO Werner Wenning, Bayer announced 1Q10 results. Sales of the Contour brand of glucose meters rose to €131 million ($181.5 million) in 1Q10, a reported increase of 5.6% or 4.6% operationally, when compared to 1Q09. In 1Q10, sales for the Breeze line of glucose meters remained constant at €30 million ($41.6 million), flat on a reported basis and up 0.7% operationally, when compared to 1Q09. The comparison to 1Q09 is a very easy one, considering Contour sales fell 3.1% while Breeze sales fell 11.8% during that quarter – though we don't know how the rest of the franchise did, we suspect it would have been directionally similar. The entire blood glucose franchise remains (by design) challenging to follow. Management noted that higher sales of the Contour line in 1Q10 contributed strongly to the growth of the Medical Care division of the Consumer Health business during the quarter, owing largely to the introduction of new product launches in Europe, particularly in Germany. Although US sales were not explicitly reported, management noted that the increased sales in Europe "more than" offset the drop in sales in the US. We were interested to see the Contour line of glucose meters declared to be the top product in the Medical Care division at Bayer. The new Didget meter hasn't been launched for long enough to show an impact in 2010 sales; we are not sure where the sales for that and the USB meter will be recognized. Interestingly, in the recently released 2009 annual report (table 4.42), there was a note that in light of current developmental status and market appraisal, the blood glucose monitoring device "COMBOMETER" is not expected to be launched before 2015.

  On the pharma side, Glucobay (acarbose) sales increased to €79 million ($109.5 million) in 1Q10, a decline of 3.7% on a reported basis or 1.7% operationally, when compared to the same quarter last year. Diabetes received little attention in the Bayer conference call, which was largely focused on Pharmaceuticals Yaz and Betaferon and Bayer Crop Science. While we did not receive any product updates, comments in the slides suggest product uptake is solid in Europe and weaker in the US. The growth of the Contour line can be seen as a win for the company in a tough SMBG market. Although it's difficult to assess the "other" line in BGM (what Bayer doesn't report, HDI, Agamatrix, etc.), when we look at the "Big 4" performance between 1Q09, 4Q09, and 1Q10, we see a major decline of 14% in the last quarter (4Q09 sales of $2.06 billion and 1Q10 of $1.77 billion) and very little growth over the last year (1Q09 sales of $1.66 billion). The "big 4" combined sales peak appears to have been in 4Q07 – we will continue to monitor the combined sales to assess the year ahead.

- **Biocon – Diabetology business grows 24% in F4Q10, driven by short acting insulin:** This morning, Chairman Kiran Mazumdar-Shaw announced F4Q10 financial results for Biocon. The Diabetology business grew 24% from F4Q09, driven by strong sales of Insugen, the company's branded short acting insulin. The diabetology division grew 24%, largely due to insulin products that grew 11% year-over-year although specific sales numbers were not provided. Sales were up significantly from last quarter and reached approximately ~$10 million from our estimates. For the year, diabetes-related sales reached $30-$40 million total, mostly from Insugen. Overall, for the year, branded formulations in diabetology (Insugen, Basalog, Glargine, and other brands) represented about $10-$20 million in sales, while insulin API sales accounted for an additional $20 million. Management did note that emerging market sales were growing and that at the end of 2010, the company would have vial and cartridge regulatory submissions in about 40 countries. Mazumdar-Shaw expressed hope that the launch of insulin pens in the second half of this year will bolster this growth figure. Biocon has entered into several new markets with its insulin products, including Brazil and Chile. It expects to launch pen-based insulin delivery devices in the second half of 2010 (this would be late 2010/early 2011 given its fiscal year). During Q&A, management noted that Biocon has obtained approval in 30 countries and is expecting to secure approval in 25 additional countries this year, and another 25 countries in the next two

years. Biocon plans to conduct a pivotal phase 3 trial in Europe later this year and hopes to launch there in 2013 or 2014. Biocon has also launched two diabetes-related awareness campaigns, the Basalog Breeze 2 program and the "Winning with diabetes" helpline. The "Winning with diabetes" campaign consists of a patient support helpline as well as a radio campaign to build awareness of self-monitoring of blood glucose. As a reminder, Biocon recently launched Bayer's Breeze 2 blood glucose meter in India after the two companies entered into an agreement in mid-2009. We are eager for sales information on this product but have heard nothing to date. Management estimated that Biocon ranked 15th in "covered" markets and 18th in the overall diabetes market. It stated an ambitious goal of reaching the top 10 companies worldwide in diabetes management by 2015.

Mazumdar-Shaw indicated that the company would be ready to provide an update on the development program for its oral insulin candidate IN-105, either in the second or third quarter. As a reminder, she stated in the F3Q10 financial update that IN-105 could be launched as early as 2011 in the Indian market. The company hopes to complete the larger phase 3 study by the end of this calendar year and secure a partnership before the end of the calendar year as well. Lastly, Biocon referenced a PricewaterhouseCoopers study that estimates the future diabetes market in India. The report projected that the total diabetes market in India will reach $30 billion by 2025 and that the future prevalence of diabetes in the country will reach 73.5 million individuals. The global market for diabetes finished 2009 at about $34 billion, according to our estimates.

- **Sanofi-aventis – Lantus sales hit $1.1 billion in 1Q10; first details on next-gen basal insulin:** In a presentation led by CEO Chris Viehbacher, sanofi-aventis announced 1Q10 results. In the first quarter reporting from the company's newly founded global Diabetes Division, total diabetes revenue reached €971 million (~$1.3 billion USD), up 11.0% operationally from 1Q09. As a reminder, sanofi-aventis announced the formation of this division in its 4Q09 earnings report, with the stated goal of surpassing Novo Nordisk in overall diabetes sales. Pursuing this strategy, the company has ramped up its investment in the US diabetes market. Currently released products contributing to sales in the Diabetes Division include Lantus, Apidra, Amaryl, and Insuman (recombinant human insulin, not sold in the US). Lantus sales rose to €790 million (~$1.1 billion USD) in 1Q10, reflecting a 5.8% increase on a reported basis and a 10.4% increase operationally from 1Q09 and up about 4% sequentially. We note that annual growth is significantly lower than growth throughout 2009, which was between 13% and 20% each quarter. Notably, during 2008, global quarterly growth ranged from 17% to 40%. Notably, management noted that the US share of voice for Lantus was being actively expanded, with substantial additions to the sales force and an increase in the budget for Lantus advertising and promotion. Operational growth was strongest outside of the US and EU, with 24.1% growth in this segment compared to 7.6% for the US and 11.4% for the EU. Growth was particularly strong in emerging markets and Japan, with operational increases of 21.3% and 40.7%, respectively (albeit from a considerably lower base). Worldwide sales of Apidra (insulin glulisine) were €39 million (~$54 million USD), with growth of 29.0% operationally and 25.8% on a reported basis from 1Q09. This reflects a 5.4% reported increase compared to the €37 million (~$51 million USD) earned in 4Q09, but accounting for currency effects this corresponds to a 1.2% decline operationally. Despite generic competition, Amaryl sales increased by 13.0% operationally and 8.0% on a reported basis from 1Q09 to €108 million ($150 million USD). This growth was driven entirely by markets outside of the US and EU.

  On the device front, management indicated that they expected the first blood glucose meter(s) jointly developed with AgaMatrix to come to market in the second half of 2010. Notably, management said the product(s) will specifically assist patients in the dosing of Lantus – and presumably the device will also further Lantus growth as it could make titration even easier. We

believe the partnership should also help AgaMatrix garner more high-frequency testers; in our latest dQ&A panel, the type 2 insulin users are testing considerably more often than the non-insulin users. The difference was significant and higher than we expected (for more information, contact Richard Wood at richard.wood@d-qa.com).

In R&D, we were glad to see that sanofi-aventis' "very long-acting" insulin analog, SAR161271, progressed to phase 2 development. SAR161271 was announced in the 4Q09 earnings report, but few details have been released. Management said SAR161271 was just entering phase 2a and planning for a submission of the long acting insulin sometime in 2013/2014 (timed for approval just before Lantus goes generic, presumably). PN2034, a non-PPAR insulin sensitizer, is slated to complete phase 2b clinical trials in 4Q10. Management reported that phase 3 results from the GETGOAL-MONO trial of lixisenatide, sanofi-aventis' once-daily GLP-1 analog, were positive and met the primary endpoint for A1c reduction. Topline results are scheduled for presentation at EASD 2010 (September 20-24, 2010). The entire GETGOAL phase 3 program is now fully enrolled, with a total of nine studies and a combined cohort of >4,500 patients. Sanofi-aventis expects to file for approval of lixisenatide monotherapy in 2H11 in Europe and 2H12 in the US. Additionally, phase 3 trials for combination Lantus and lixisenatide are expected to begin in 4Q10. Sanofi-aventis plans to integrate the delivery of the two drugs with a single device.

- **BMS – Onglyza sales continue to disappoint at $10 million in 1Q10:** CEO Lamberto Andreotti led the BMS 1Q10 financial update this morning. Worldwide sales of BMS/AZ's Onglyza (saxagliptin) came in below expectations at $10 million for 1Q10 ($6 million from the US and $4 million from international markets). As a reminder, Onglyza sales reached $20 million in 3Q09 after mid-quarter approval and dropped to $4 million in 4Q09 due to stocking orders. Management acknowledged that Onglyza's performance was below company projections; however, they cited week-over-week increases in new/naïve prescriptions as a share of the DPP-4 market (roughly 6%) and the number of new physicians prescribing Onglyza (approximately 20,000). Nevertheless, the growth of Onglyza is disappointing, particularly compared to the early success of Merck's DPP-4 inhibitor Januvia (sitagliptin), which achieved sales of $42 million in its first quarter on the market (4Q06). While this difference highlights the impact of being first-to-market, the DPP-4 inhibitor class is also perceived to have a number of undifferentiated drugs. Management was humble about its experiences, acknowledged the disappointment and indicated that it would continue to work on this front. Andreotti referenced a number of studies that show the declining role of sales forces versus the influence of the access team as well as the medical education team; he concluded " …so that's where you need to spend more time and more people".

  In other news, the FDA has accepted a supplemental NDA application for a fixed dose combination of Onglyza and metformin and issued a PDUFA date of October 29, 2010. As this compound is also undifferentiated from Janumet, we do not expect BMS/AZ to show differentiation here. On the SGLT-2 front, one phase 3 study of dapagliflozin will be presented at ADA this year evaluating the SGLT2 inhibitor as an add-on to insulin therapy. We are keen to see this research because the combination could be synergistic. In addition, data from studies evaluating dapagliflozin as an add-on therapy to sulfonylurea and an add-on therapy to metformin vs. sulfonylurea will be presented at EASD in September 2010. In the Q&A, Chief Scientific Officer Elliot Sigal clarified that the rates of urinary tract infections (UTI) have been "roughly similar" to placebo in the phase 3 program for dapagliflozin, whereas the rates of genital infections, particularly candida infections, have been higher than placebo. Going forward, BMS is focused on building awareness of Onglyza by fine-tuning its message to endocrinologists and launching a patient education and direct-to-consumer marketing campaign; interestingly, a TV campaign will be launched in May (presumably 2011). (FYI I've seen Onglyza commercials on TV on the east coast - is this date correct?)

- **EnteroMedics – IDE submitted for second-generation Maestro RC system:** EnteroMedics recently reported financial results for 1Q10. The company recorded a net loss of $4.7 million and R&D expenses of $2.4 million, primarily attributable to clinical trials for the company's VBLOC vagal nerve blocking therapy with the Maestro system. As of March 31, 2010, EnteroMedics had cash, cash equivalents, and short-term investments totaling $14.6 million. Management believes this current cash balance, along with a recently completed equity financing of $4.8 million, will provide resources to continue operations into the second half of 2010.

  After discussing the results of the EMPOWER study with the FDA in early 1Q10, the company filed an investigational device exemption (IDE) application on March 15, 2010 for its next-generation Maestro RC system for the treatment of morbid obesity using VBLOC therapy. This IDE will allow EnteroMedics to use the second-generation Maestro system in clinical studies to obtain data required to support a potential premarket approval (PMA) application. Also in March, EnteroMedics appointed Dr. Scott Shikora, Chief of General Surgery, Bariatric Surgery, and Minimally Invasive Surgery at Tufts University School of Medicine, as the Consulting Chief Medical Officer.

  As a reminder, management recently announced additional data from the EMPOWER study, which failed to meet the primary and secondary efficacy endpoints, and preliminary results from the ENABLE trial at the JP Morgan Healthcare Conference in January 2010. Also at this conference, management indicated that re-conducting the EMPOWER trial would cost $10-15 million (roughly the cost of the initial EMPOWER study). For more information on the data released at the JP Morgan Healthcare conference, please see our coverage from the January 16, 2010 issue of Closer Look. While we do continue to look forward to six-month data from the ENABLE trial, which the company had previously planned to announce in 1Q10, and further details on the design of clinical studies for the second-generation Maestro system, we also note that there seems to be little confidence in the company, given the disappointing previous results and trajectory.

- **Sanofi-aventis – Announces plans to introduce blood glucose monitors in India in 2011:** Recently, sanofi-aventis announced plans to introduce blood glucose monitors in India in 2011. In addition to urban areas, the company plans to work with local governments to make its products available in rural parts of the country; global head of the diabetes division, Pierre Chancel, noted that sanofi-aventis "will offer customized solutions, [meaning] the right product at the right price corresponding to the right location." Given the widespread poverty in rural India, we assume sanofi- aventis products will be sold at a significant discount in rural areas of the country. Currently, the diabetes market in India is roughly Rs. 2,000 crores ($427 million). According to the senior director of the cardiometabolism unit at Aventis (the local unit of sanofi-aventis), Susheel Umesh, Lantus (insulin glargine) currently generates Rs. 50 crore ($10.7 million) in revenue in India (with 10% market share), growing at roughly 33% annually.

- **Amylin – Metreleptin receives an orphan drug designation for the treatment of lipodystrophy; Amylin plans to file NDA for metreleptin in 2010:** Recently, Amylin revealed plans, through its 10-K filing, to develop metreleptin for patients with severe lipodystrophy. Lipodystrophy is a rare life-threatening metabolic condition characterized by the defective regulation of adipose tissue and a loss of subcutaneous fat. In addition, patients with lipodystrophy secrete insufficient amounts of leptin, a hormone that acts on the hypothalamus to regulate food intake and energy expenditure. Interestingly, Amylin has found that leptin replacement therapy can be a life-saving treatment for these patients and has received an orphan drug designation from the FDA for metreleptin, a recombinant form of human leptin. As a reminder, orphan drugs are agents that treat rare medical conditions, affecting less than 200,000

individuals in the US (as we understand it, the number of patients in the US with lipodystrophy are in the thousands, rather than tens or hundreds of thousands) Orphan designations also qualify the sponsor for tax credits and marketing incentives. Metreleptin is being developed as part of Amylin's Integrated Neurohormonal Therapy for Obesity (INTO) strategy. Amylin obtained exclusive rights to the leptin franchise from Amgen in 2006. However, Amylin may be required to pay royalties on product sales and make milestone payments depending on the developmental and regulatory success of metreleptin. Metreleptin has already been approved for patients with lipodystrophy and "related metabolic abnormalities" under a special treatment IND protocol. Amylin plans to file an NDA for metreleptin in 2010; as we understand it, the company is currently working with the FDA on a timeline for metreleptin and may be able to submit a rolling NDA, which would allow for an expedited review process. Finally, from a commercialization perspective, Amylin plans to leverage its relationship with endocrinologists (from Byetta and Symlin) to build awareness of metreleptin to treat lipodystrophy.

- **Takeda – Provides update on Actos patent litigation and generics timeline:** As a follow-up to litigation filed in July of 2009, Takeda recently announced the settlement of six out of eight patent infringement suits filed by the company against several manufacturers intending to produce generic Actos (pioglitazone) and generic ACTOplus met (Actos plus metformin), as the patent for the blockbuster drug is set to expire in 2011. According to the settlements reached, generic Actos will enter the US market on August 17, 2012 and ACTOplus met will enter the US market on December 14, 2012. There are still two unsettled cases with ongoing litigation against Teva Pharmaceuticals and Aurobindo Pharma Limited, and the company has emphasized the entry of generic Actos and ACTOplus met will remain uncertain until these lawsuits are settled. Although additional companies may choose to file abbreviated new drug applications (ANDAs) for generic Actos products (it appears two additional companies already have), the company remains committed to and confident about defending and enforcing its patents. As a reminder, Takeda's Actos franchise generated $4.1 billion in revenue in calendar year 2009, compared to $1.1 billion for GSK's Avandia franchise.
- **Roche – Study finds Lucentis superior in treating Diabetic Macular Edema compared to laser therapy:** Dr. Michael Elman and colleagues published the results of a trial evaluating the effectiveness of Lucentis (Genentech/Roche's ranibizumab) in Diabetic Macular Edema (DME) in the journal Ophthalmology. The study recruited 691 patients with visual acuity and DME and a total of 854 "study eyes." Patients were assigned to receive focal/grid laser treatment either with or without Lucentis treatment. In summary, after one year of follow-up, roughly 50% of those treated with Lucentis demonstrated significant improvements in visual acuity (of at least two lines on an eye chart) compared to 28% of those who did not receive Lucentis treatment. Fewer patients in the Lucentis arm (3-4%) experienced visual loss (of at least two lines on an eye chart) compared to the laser-only arm (13%). There were also no serious risks associated with 7the intravitreal injections of Lucentis; roughly 1% of Lucentis-treated patients experienced an eye infection. As a reminder, Lucentis has been approved for the treatment of neovascular (wet) age-related macular degeneration (AMD) in 2006 and has recently been submitted to the FDA for the treatment of DME in December 2009. Investigator Dr. Neil Bressler characterized this study as "definitive proof" of superiority of Lucentis against laser therapy and urged the consideration of off-label use of Lucentis for the treatment of DME; he noted that Lucentis could be "the first new treatment for DME in over a quarter of a century." As a reminder, Genentech has outlicensed Lucentis to Novartis, which holds exclusive rights to develop and market ranibizumab outside the US.

  From a commercial perspective, sales of Lucentis have suffered cannibalization from off-label use of Genentech/Roche's Avastin (bevacizumab), a monoclonal antibody derived from the same

antibody as Lucentis and FDA-approved for the treatment of metastatic cancer. In a recent Form 10-K filing for Genentech, decline in Lucentis prescriptions among newly diagnosed wet AMD patients was attributed to the off-label use of Avastin. It is important to note that Avastin has a significant price advantage, costing between $20 and $100 per dose, compared to Lucentis, which costs approximately $2,000 per dose. As we do more research in this area, we will try to learn more about how many physicians are using Lucentis and Avastin off-label for the treatment of DME. We expect to hear great enthusiasm about these results; that this therapy could be truly disease-modifying is exciting, indeed.

- **Living Cell Technologies – Announces Russian phase 1/2a trial results with DIABECELL:** Living Cell Technologies (LCT) recently announced preliminary phase 1/2a results of DIABECELL, the company's novel islet product for the treatment of type 1 diabetes. As a reminder, DIABECELL consists of alginate-encapsulated porcine glucose responsive/insulin-producing islets. LCT stated that DIABECELL could be injected laparoscopically into patients' peritoneal cavities under local anesthesia and that the product's encapsulation technology bypasses the powerful immunosuppression regimen regularly required in xenotransplantation. In the three-year Russian trial, eight patients with type 1 diabetes (ages 21-68 years) received one to three transplants of 5,000 or 10,000 IEQ per kg body weight DIABECELL over the course of 18 months. We presume dosing and repeat implants were determined as needed to promote safety and efficacy although detail wasn't made available. At six-month follow-up post first implant, six of eight patients exhibited A1c declines between 0.2%-2.8%; these six patients additionally showed between 13%-100% declines in daily insulin dose requirements. Of the three patients that have reached 18-month follow-up post first implant, two exhibited A1c declines between 0.9%-1.3%, with reduced insulin requirements between 10%-100%. Baseline and mean declines in A1c and insulin requirements were not reported, making it difficult to draw conclusions about the magnitude of the treatment's impact. LCT indicated that the longest continuous period of complete insulin discontinuation was 14 weeks.

  We see these results as positive progress for DIABECELL's encapsulation technology; LCT indicated the trial confirmed the safety and tolerability of the product as well, with no evidence of porcine endogenous retrovirus RNA or DNA (indicative of pig-to-human transmission of diseases) and with only two patients experiencing abdominal discomfort post implantation. However, given the limited success of transplant technologies thus far, we remain skeptical of this treatment's long term potential. We look forward to more detailed results from all patients in the trial in order to better identify for which patients and which dosing regimens DIABECELL was most successful. Follow-up results are scheduled for oral presentation at ADA in June. While porcine cells currently appear to offer the most commercially viable source of islet cells, regulatory agencies have thus far been wary of approving the implantation of non-human cells because of worries about transfers of porcine pathogens. A phase 1/2 trial investigating higher doses of DIABECELL (ClinicalTrials.gov ID: NCT00940173) in New Zealand is estimated to be completed in January 2011.

- **Novo Nordisk – Victoza sales reach ~$70 million for 1Q10; progress in pipeline:** In a call this morning led by CEO Lars Sorenson, Novo Nordisk announced 1Q10 earnings. In total, Diabetes Care rose to DKK 10.2 billion ($1.90 billion USD) in 1Q10, up 11% on a reported basis or 13% operationally when compared to 1Q09. As expected, modern insulins continued to drive growth in 1Q10 at DKK 5.9 billion ($1.1 billion USD), rising 17% on a reported basis or 20% operationally and accounting for 69% of the company's total sales. Levemir sales in 1Q10 rose to DKK 1.5 billion ($282 million USD), a reported growth of 31% or 33% on an operational basis. NovoRapid grew to DKK 2.6 billion ($487 million USD), 15% on a reported basis or 18% operationally – annualizing at nearly $2 billion is certainly big progress given that the drug was

under $1 billion in sales exiting 2006. NovoMix rose to DKK 1.7 billion ($322 million USD), 11% on a reported basis or 13% operationally. Notably, management noted a stalling in the insulin market in the EU, stemming predominantly from increased penetration of GLP-1 analogues. While management suggested this was "of temporary nature," we will watch closely to see if insulin sales will continue to slow as GLP-1 uptake increases (possibly matched in the US as the incretin battle plays out), particularly as new candidates enter the market. That said, insulin sales in the US were bolstered by price increases as well as other factors. Also of note, Victoza sales were broken out for the first time in 1Q10, reflecting a vote of confidence from Novo Nordisk – at DKK 370 million ($69 million USD). Organic sales for Victoza used this quarter were likely just above $20 million; US sales were boosted by DKK 250 million ($47 million USD) in supply chain pipeline filling (i.e., inventory) in connection with the recent US launch. Management's recap reflected that uptake in the US thus far has been solid, with Victoza cornering 23% of new prescriptions and 11% of total prescriptions in the GLP-1 market since launch in February 2010. Given that Byetta prescriptions fell only 7.7% in the quarter, we suspect new market uptake has been taking place primarily in patients naïve to GLP-1 therapy, indicating substantial room for the market to grow.

CSO Dr. Mads Thomsen led the research and development update for Novo Nordisk. As of 1Q10, the company initiated seven out of eight trials in the phase 3a program for BEGIN and BOOST for degludec and degludec plus, respectively. The plan is still for the NDA to be filed with the FDA in early 2012. One clear message is that no time is being wasted pushing forward new insulins degludec and degludecPlus; as a reminder, insulin degludec is a new long-acting insulin and degludecPlus is a fixed combination of a rapid-acting insulin and insulin degludec. Over 8,000 patients have been enrolled in these trials to date. These trials compare degludec and degludecPlus to insulin glargine and evaluate a once daily dose as well as a three-times weekly dose of insulin degludec. Management expects to initiate the final phase 3a study in 2Q10. Notably, during the Q&A, Thomsen suggested that phase 2 studies for insulin degludec have demonstrated improvements over modern insulins that are on par with the improvements between modern insulin and human insulins (30-35% reductions in hypoglycemia). He also highlighted the dosing flexibility of insulin degludec, noting that it can be administered in the morning or evening, with "no strings attached," as well as the potential for three-times weekly dosing. Novo Nordisk is also aggressively pursuing several exciting early-stage compounds. It recently completed a phase 1 study of the "fixed ratio combination" of insulin degludec and Victoza (NN9068). Thomsen indicated that the initial results were encouraging and "support full product development." In addition, during Q&A, he described the possibility of "piggybacking" on the degludec safety database and the Victoza registration to move this combination directly into phase 3 studies by 2011. The company is currently in discussions with regulatory agencies to explore the feasibility of this strategy. In other news, Novo Nordisk recently initiated a phase 1 trial for an oral GLP-1 analog and filed Prandimet (fixed dose combination of repaglinide and metformin) with the SFDA in China.

- **Edwards Lifesciences – Comments on EU trials bode well for US launch of in-hospital CGM product:** In a call led by CEO Michael Mussallem, Edwards reported 1Q10 results. Management briefly referenced the company's partnership with DexCom during its prepared remarks, reaffirming that the in-hospital continuous glucose monitoring (CGM) system was continuing post-approval trials in a limited number of centers in the EU. During the Q&A, Mussallem noted that Edwards was looking to gain confirmation in these trials that the system was accurate in a variety of settings as well as easy to use. He also pointed out that the EU launch was a relatively early model, and thus the company would use the experience to gauge what additional features would be needed for the commercial launch. However, Mussallem did imply

that the first-generation sensor would be filed in the US; presumably a later generation would be launched.

- **Abbott — Modest rebound in sales of 3.9% for Diabetes Care in the first quarter:** Abbott reported Abbott Diabetes Care (ADC) 1Q10 results in a call led by CFO Thomas Freyman. In Diabetes Care, global sales of $295 million rose 3.9% on a reported basis, or fell 1.5% operationally, when compared to 1Q09. Management had forecast "mid single digit" growth in 2010 and this came in at the low end. We note this quarter is a very easy comparison to 1Q09, which saw losses of 12.6% worldwide, 12.1% in the US, and 12.9% internationally. In 1Q10, US sales rose 2.6% to $123 million while international sales rose to $172 million—a 4.8% reported gain though a 4.4% operational loss. As expected, CGM revenues were not reported separately and we estimate that this business sold perhaps in the vicinity of $1 million, but admittedly this is a guess—the company has stopped shipping CGM receivers and transmitters due to some operational difficulties and we assume this will impact their sensor business and reliability perceptions overall. Notably, we do think management has acknowledged that CGM is the way of the future, even if it is a lower profitability business and we do believe they are working on next-generation functionality, though this will take some time to get through this FDA once it is ready to submit. Outside of the top-line financial announcements, the call was almost entirely absent of further commentary on the diabetes business. Management did mention that going forward, the focus in the diabetes business would be to improve profitability, a strategy adopted for the diagnostic division a few years ago and one they have mentioned before. For 2Q10 management forecasts mid-single digit reported growth for the Diabetes Care business – we assume this should be achievable particularly because 2Q09 is another easy comparison as the business fell 8% in that quarter.
- **J&J —Diabetes care business up 10.4% in 1Q10 on an easy comparison:** J&J announced 1Q10 results in a call led by CFO Dominic Caruso. LifeScan/Animas (Diabetes Care Franchise) sales were $597 million worldwide in the first quarter, up 10.4% on a reported basis and up 6.4% operationally, on an easy comparison (global sales fell 12% in 1Q09). US sales rose to $290 million or 7.4%, while international sales rose 13.3% on a reported basis (5.4% operationally) to $307 million. Both comparisons were easy, as 1Q09 US and international sales had declined 11% and 13%, respectively. Although sales are not broken out separately, Animas, the insulin delivery division of J&J, achieved double-digit growth. It is difficult to know if that is closer to 10% or 20% or higher, but our dQ&A patient panel data suggests Animas is doing very well in terms of winning a much higher percentage of "new" pumpers relative to its overall market share in the last couple of quarters in particular (dQ&A subscribers will receive this data shortly; for information on subscribing, please contact richard.wood@d-qa.com).

  On the blood glucose monitoring side, management cited improved volume growth offset by continued pricing pressure as contributors towards this quarter's results. Despite the easy comparison, J&J's 1Q10 results are impressive, considering that the first quarter is historically low for the diabetes device/technology space. Management noted that the diabetes technology market has experienced stabilization, if not rebound, in the first quarter. Unfortunately, no further updates were given on the diabetes technology pipeline, although new supplemental device pipeline materials suggest that the CGM sensor-integrated insulin pump (produced in collaboration with DexCom) is slated for submission in 2010. We have heard very positive reflections about this system, which was launched in the Netherlands earlier this year as we understand it. As the name suggests, higher accuracy is a key feature, designed to be higher than the current ISO standards; portability is also characterized by some as noticeably better. While historically accuracy has not necessarily been a top priority from all patient segments (patients

didn't necessarily realize their meters could be up to 20% "off"), recent focus by the FDA has increased awareness and concern about this issue.

- **Novartis – Galvus/Eucreas continues strong growth in 1Q10; further pipeline updates:** CEO Joseph Jimenez led the 1Q10 financial results for Novartis. Galvus/Eucreas sales in 1Q10 were $76 million, up almost three-fold from $26 million in 1Q09 and up 15% from $66 million in 4Q09. Management cited particularly strong growth of the DPP-4 inhibitor in Germany, Spain, Brazil, Korea, and India. While diabetes was not explicitly mentioned in the prepared remarks, we noticed several updates to the company's pipeline. Novartis expects to begin phase 3 trials for an anti-IL-1 beta antibody Ilaris (ACZ885) by December 2010, with an anticipated NDA submission in 2012. As a reminder, this compound is in phase 2 studies for type 2 diabetes and is already approved for the treatment of cryopyrin-associated periodic syndrome (CAPS); several other companies are also exploring the potential of anti-IL-1 beta antibodies to improve glycemic control and other cardiometabolic risk factors, including XOMA (XOMA 052), Eli Lilly (LY2189102), Amgen (AMG 108), and Cytos Biotechnology (CYT013-IL1bQb). Novartis also provided an update on LCQ908, a DGAT1 (diacylglycerol acyltransferase 1) inhibitor in phase 2 studies for the treatment of type 2 diabetes. The company plans to announce interim results from phase 2 studies in the second half of 2010 (with a potential NDA submission in 2013). Preclinical studies have shown that DGAT1 inhibitors modify lipid metabolism and prevent diet-induced obesity.
- **Amylin – Byetta sales fall 5% in 1Q10:** CEO Daniel Bradbury led the 1Q10 financial results for Amylin. On an exciting note, Bradbury also announced that Eli Lilly has submitted a Marketing Authorization Application (MAA) to the EMEA for Bydureon. On the financial front, net product sales fell below expectations at $172.3 million in 1Q10, falling 3.9% from $179.3 million in 1Q09. Byetta sales declined 5.2% to $149.8 million for the quarter, down from $157.7 million for the same period last year. Sales declined 8% sequentially. Symlin sales rose to $22.5 million in 1Q10, up 4.2% from $21.6 million in 1Q09 and up about 9% sequentially, reflecting a recent price increase. Despite the disappointing sales, these figures bode well for previous promises made by management; the company is on track to reach sustainable positive non-GAAP operating cash flow by the end of 2010 and to achieve positive non-GAAP operating income as well as GAAP operating profit in 2011. Cash at quarter end was just under $600 million.

  For Byetta, this is the lowest recorded revenue in two years. We still believe that weakness for both Byetta and Symlin stems from lack of optimal training on titration and challenging perceptions in the marketplace concerning complexity. Management noted that the GLP-1 market has grown 60% in the previous eight weeks, suggesting that the prescription loss of only 7.7% by Byetta in the quarter reflects the drug is not losing substantial market share to new competitor Victoza (Novo Nordisk's liraglutide) and there is room for growth in the market—good news for Bydureon, pending approval. Assuming it isn't too complex, we expect Bydureon with once-weekly dosing and better tolerability to increase the market substantially. Interestingly, in our most recent dQ&A survey, there was nearly 10% awareness of Victoza by the current Byetta users and ex-users in the panel.

  On the R&D front, the development of a Bydureon pen remains on track with an anticipated launch in late 2012 or early 2013, pending FDA. Notably, Amylin is planning to initiate a phase 2 proof-of-concept study later this quarter for a monthly-dose suspension formulation of exenatide. This suspension does not require reconstitution and leverages Alkermes' Medisorb technology. The primary goal of this phase 2 study will be to evaluate the safety, efficacy, and tolerability of this formulation of exenatide. The CV study will begin shortly with 9,500 patients rather than 12,500 patients.

- **Eli Lilly – Humalog posts solid 12% growth in 1Q10; basal insulin candidate moves to phase 2:** In a call led by CFO Derica Rice, Eli Lilly announced 1Q10 results. Total diabetes-related revenue of $922 million rose 11.2%. Humalog posted solid 12% growth in the quarter, with revenue reaching $506.4 million in 1Q09, driven by international sales –management attributed this to higher demand and the favorable impact of foreign exchange. The Humalog comparison was a challenging one as total sales in 1Q09 had risen 11%. Humulin sales were $257.8 million in 1Q10, rising 7% from $240.6 million in 1Q09, boosted by strong US sales, which management attributed to increased prices – in contrast to previous quarters, no mention was made of reduced demand. While management indicated reduced demand in international markets, we expect demand to increase in the coming quarters, driven by developing regions – in the Q&A, management reiterated efforts to increase promotion of the diabetes portfolio in China, including a recent doubling of the sales force there (we are uncertain from what base). We note that this is particularly timely as prevalence continues to grow in the region –recent increased estimates in NEJM suggest roughly 92.4 million adults have diabetes and 148.2 million adults have prediabetes in China, with animal insulin remaining the insulin of choice. Total Lilly-recognized revenue for Byetta in 1Q10 was $115.7 million, up 19% from $97.5 million in 1Q09. In the Q&A, management indicated some initial market share loss to Novo Nordisk as Victoza continued rollout in the US and EU, particularly amongst endocrinologists aiming to gain experience with the new GLP-1 – we suspect Byetta sales will remain relatively flat at best until the release of Bydureon.

  The company's much-needed basal insulin candidate LY2605541 also moved into phase 2 trials in 1Q10, a clear positive for the Lilly's insulin portfolio. However, it is still unclear how Lilly will attempt to differentiate its basal insulin from current competitors – in the Q&A, management only detailed that the candidate evidenced a flat 24-hour profile in phase 1 trials and did not disclose any plans (yet) to investigate the combination of its GLP-1 offerings with LY2605541, a combination both sanofi-aventis and Novo Nordisk are currently pursuing (and that we assume Lilly will eventually pursue). Finally, as predicted in the 4Q09 earnings report, GLP-1 Fc initiated the full phase 3 program AWARD in 1Q10. We are still curious to see how Lilly will move forward with GLP-1 Fc in the wake of Bydureon – it is still unclear if the company will pursue an ambitious superiority strategy. Clinicaltrials.gov indicates that there are currently two recruiting phase 3 trials, AWARD-1 (vs. exenatide or placebo for 52 weeks in patients on metformin and pioglitazone) and AWARD-2 (vs. insulin glargine for 78 weeks in patients taking metformin and glimepiride), as well as a past phase 2/3 trial comparing LY2189265 with sitagliptin.

- **Takeda – Alogliptin and fixed dose combination of Actos/metformin approved in Japan:** Takeda has received approval from the Japanese Ministry of Health, Labor, and Welfare for Nesina (alogliptin benzoate) and Metact (fixed dose combination of pioglitazone and metformin). Nesina, previously known as alogliptin or SYR-322, is a DPP-4 inhibitor to be taken once daily in a 25 mg dose. Nesina is indicated for use when patients fail to achieve adequate glycemic control with diet and exercise alone or when lifestyle in combination with an alpha-glucosidase inhibitor (such as Takeda's Basen or voglibose) fails to achieve adequate glycemic control. Metact will be sold as a fixed-dose combination of either 15 mg of Actos and 500 mg of metformin or 30 mg Actos and 500 mg of metformin, in patients where the concomitant therapy of Actos and metformin is appropriate. As a reminder, alogliptin failed to receive FDA approval in the US (NDA originally filed December 2007) and has required the company to undertake an extensive multi-year cardiovascular safety trial (EXAMINE) to explore the safety of the DPP-4 inhibitor in patients with previous cardiovascular events. Takeda has recently submitted several NDAs or NDA supplements to the Japanese Ministry of Health, and in addition to the two drugs recently approved, there are pending applications for use of alogliptin in combination with TZDs.

Although these applications were submitted more recently, we are unclear if more information will be required for the Japanese Ministry to make its decision on use of alogliptin in combination with TZDs. The approval of alogliptin in Japan is certainly positive news for Takeda, although the drug will face competition from previously established Januvia (Merck's sitagliptin) and Onglyza (AZ/BMS saxagliptin). Januvia was approved in Japan in late 2000; however, Takeda will benefit from years of marketing Actos – so this market bears close watching. Onglyza has yet to be approved in Japan and as a reminder, the global BMS/AZ agreement excludes Japan – there, BMS is engaged in a licensing agreement with Otsuka Pharmaceutical.

- **Roche – Strong 1Q10 growth in diagnostics driven by Diabetes Care:** In a call led by CEO Severin Schwan, Roche reported 1Q10 earnings results. Roche Diabetes Care sales grew substantially above market in 1Q10 to 708 million CHF ($670.1 million), a reported growth of 4.3% or 13.0% operationally – up from 679 million CHF ($593 million) in 1Q09. This represents a marginally soft comparison as 1Q09 saw reported losses of -2.9% and operational losses of -9.2%. Management noted that global sales were negatively impacted by weakening of the US dollar, the Euro, and the Japanese Yen during the quarter. Sales in the US were 173 million CHF ($163.7 million), down 3.9% year over year. While this is a tough comparison in relation to the 22.4% growth achieved in 1Q09, we note 1Q09 was positively impacted by a substantially stronger US dollar and a very soft comparison to 1Q08 sales declines of 31.6%. International sales in 1Q10 grew to 535 million CHF ($506.4 million), up 7.2% on a reported basis or 16.3% operationally. This represented an easy comparison to 1Q09 declines of 9.6% reported and 15.5% operational. According to management, 1Q10 growth in Diabetes Care was driven by continued strong sales of Accu-Chek Aviva Nano and Accu-Chek Performa Nano. Continued strong market uptake for the Accu-Chek Mobile and Accu-Chek Combo systems has also been key, and management noted 1Q10 saw double-digit growth in insulin delivery revenue, as has been the case for several quarters now. Upcoming in the second half of 2010, management expects to launch the Accu-Chek Aviva Nano in the US; however, previous plans to launch the Accu-Chek Combo in 2010 appear to have been dropped. No further details were given regarding the recent acquisition of Elron's Medingo and the Solo Patch Pump; however, management mentioned the focus will be on improving the manufacturing process for the device prior to a 2012 launch. Management expects Diabetes Care diagnostics to continue to perform substantially above market for the rest of 2010. Given that the market declined in 2009 by about 3% according to our estimates, we aren't sure what that means.

  Management briefly highlighted that detailed results from T-emerge 1, 2, 4, 5, and 7 phase 3 trials would be presented at ADA 2010 in June, with an expected filing still delayed to 2011. As noted at the company's Investor Day in March, phase 3 CV outcomes trial ALECARDIO for PPAR alpha-gamma dual agonist aleglitazar enrolled its first patient in 1Q10. However, we still await results from the phase 2 renal function study SESTA-R, previously promised in 1Q10 – the company's slides now estimate publication in 2Q10. Lastly of note, Bayhill Therapeutics' phase 1 proinsulin treatment for type 1 diabetes RG7426 now expects a phase 2 "go/no-go" decision in 2Q10 – based on preliminary phase 1 results presented at ADA last year, we still see RG7426 as one of the more promising diabetes vaccines in clinical development and would be very surprised if this were not continued to phase 2.

- **Pfizer – Announces an increased focus on Asia-prevalent diseases:** Recently, Pfizer announced plans to focus R&D efforts on diseases prevalent in Asia. President of R&D Martin Mackay expressed a special interest in diabetes noting that Pfizer plans to "apply the science and come up with diabetes medicines exclusively for Asians." The company has organized a massive clinical research unit in Singapore with 14,000 healthy volunteers who will be involved in Asia-specific research. While diabetes was not extensively discussed, we are excited to hear about a

renewed interest in diabetes from Pfizer, especially given the recent discontinuation of its DPP-4 inhibitor candidate PF-00734200 in phase 2 studies from the pipeline. In addition, this investment in Asia will certainly help Pfizer achieve its goal of increasing overall market share in the Chinese pharmaceutical market from 4% to 6%. As a reminder, Pfizer recently entered into an agreement with Takeda in December 2009 to co-promote Actos (pioglitazone) in China.

- **Sanofi-aventis – Partners with CureDM to acquire rights to Pancreate:** Delaware-based CureDM announced that sanofi-aventis has agreed to acquire worldwide exclusive rights to develop, manufacture, and commercialize Pancreate (proisletide acetate), also known as Human proIslet Peptide (HIP). Pancreate is a conserved 14-amino acid segment of the REG3a gene, which is responsible for stimulating the differentiation of pancreatic progenitor cells into functional islet cells. In preclinical studies, Pancreate administration has resulted in the production of new insulin-secreting islet cells in mice; initial research also suggests that the REG3a gene may play a rate-limiting step in islet neogenesis and progenitor cells (that can differentiate into islet cells) may compartmentalize to the ductal portion of the adult human pancreas. Under the terms of the agreement, sanofi-aventis will make a series of payments (upfront cash payment and developmental, regulatory, and sales milestones) totaling up to $335 million. If Pancreate is approved and marketed, CureDM will also receive increasing royalties on worldwide sales. The company expects to file an IND for Pancreate later this year and hopes to initiate clinical studies in both type 1 and type 2 diabetes patients.
- **Orexigen – Corrects COR-II trial data for categorical weight loss:** Orexigen filed a Form 8-K with the SEC that included revised COR-II (NB-303) trial data for Contrave as well as a 66-page slide presentation on Orexigen's obesity program and the overall "partnerability" of the company. In the previously released COR-II data, the company did not "apply the intended weighting to those patients re-randomized to Contrave32." Therefore, in the intent-to-treat, last observation carried forward (ITT-LOCF) analysis, 50.5% of patients (as opposed to 56.5%) lost ≥5% body weight and 28.3% of patients (as opposed to 32.9%) lost ≥10% body weight after 56 weeks. In the "completers" analysis, 64.9% of patients (as opposed to 75.8%) lost ≥5% body weight and 39.4% (as opposed to 48.2%) lost ≥10% body weight after 56 weeks. Although the proportion of patients achieving ≥5% and ≥10% body weight loss has been revised downward, the data continue to satisfy the FDA's categorical efficacy benchmark. During the Q&A session in Orexigen's recent 1Q10 financial update, management confirmed that the mistake in the Contrave NDA was discovered during due diligence with a potential partner and they do not expect this to affect the review or approvability of Contrave.
- **Repros Therapeutics – Responds to FDA feedback on phase 2 trial design for cross-over drug Androxal:** Recently, Repros Therapeutics responded to feedback received from FDA regarding phase 2 trial design for Androxal (enclomiphene) as a treatment for type 2 diabetes. Androxal is an oral drug candidate in phase 2 development for the normalization of testosterone and luteinizing hormone levels. Retrospective analyses of phase 2 results indicated a potential lowering effect on fasting glucose levels (a significant median reduction of >10 mg/dl with both the 12.5 and 25 mg doses in approximately 20 subjects with elevated blood glucose), prompting Repros to investigate the drug for the treatment of type 2 diabetes. FDA feedback recommended the company increase the sample size (from 20 subjects per arm to 40-50 subjects per arm) in its proposed phase 2 trial, as well as clarify the exclusion criteria and protocol design. Assuming the trial confirms Androxal's glucose-lowering effects, Repros has proposed two further clinical studies and also plans to apply the safety database from trials in secondary hypogonadism toward the diabetes indication (the company suggested roughly 20% of patients in these trials had type 2 diabetes).

There was no mention of start date for the proposed phase 2 trial, and management indicated additional capital would first need to be raised to fund the study. In our view, it is still unclear what the broader potential of Androxal will be or if the trial will confirm a clinically significant effect – we also hope to learn more about the side effect profile of Androxal. In previous trials, the most common adverse events for men on Androxal were headaches in 3.6% of subjects, hot flashes in 2.5%, and fatigue in 2.5%.

- **Access Pharmaceuticals – Plans clinical trials with oral insulin candidate:** Dallas-based Access Pharmaceuticals recently announced plans to initiate clinical trials with its oral insulin candidate. As background, the candidate uses Access's oral drug delivery technology, which binds insulin to cobalamin (vitamin-B12) to enhance absorption in the intestines; early preclinical trials suggested slightly lower declines in blood glucose compared to subcutaneously delivered insulin (about 80% of that achieved by subcutaneous delivery), though over a prolonged time course (maximal declines in blood glucose at about five hours after administration versus less than one hour with subcutaneous insulin). While few details were provided on the planned trials, management suggested phase 1 trials would be completed in about nine months and would be conducted overseas to reduce costs.
- **PositiveID – Launches second-stage of development for iGlucose system:** Florida-based PositiveID recently announced that it has launched the "second-stage" of development for its iGlucose system. The iGlucose system is a standalone device that can connect to a data-capable blood glucose meter and send blood glucose data to an online database via encrypted text messaging. The device has a microprocessor, memory (RAM), a minimal user interface, a GSM (cellular) modem, an internal antenna, and a battery; these components allow the device to automatically send blood glucose readings to an online database without a cell phone, a telephone line, a wireless network, or a computer. PostiveID is creating a system, in which the iGlucose data can be sent to physicians and caregivers at specified time periods. The second-stage of development will involve miniaturizing the device into a small "cradle" that will be able to directly connect to glucose meters. PositiveID plans to complete a prototype of the iGlucose system during the second half of 2010. The company has partnered with Bit7, which will be responsible for the hardware development (mechanical and electrical engineering), and IsoSoft Solutions, which will be responsible for the software development (data flow and communications with the central server). We look forward to further updates on the iGlucose system, especially if it can encourage retrospective analysis of blood glucose trends and more frequent testing. While we believe this type of system will certainly reduce the barriers associated with analyzing patient data, the current incentives of the healthcare system support office-based physician care and it remains to be seen whether physicians will be able and willing to use such a system.
- **BMS/AZ – Announce plans to launch Onglyza (saxagliptin) in India:** The Indian divisions of Bristol-Meyers Squibb and AstraZeneca announced a partnership to commercialize DPP-4 inhibitor saxagliptin (marketed as Onglyza in the US and EU) in India. The drug will be marketed for roughly one-fifth of the US cost (roughly $5 per 5 mg daily dose in the US), similar to prices for Merck's sitagliptin (which we estimate at about Rs. 43/$0.96 USD per pill), which launched in India in July 2008. In our view, it is still unclear if the average patient with diabetes in India (there are estimated to be approximately 27 million patients with diabetes in India) will be able to afford this price point; however, while Merck does not break out Januvia sales by region, international sales have been strong, at $168 million in 4Q09. We will hope to find out more over time as to whether the emerging markets are driving this growth. Notably, under the alliance, BMS/AZ India have also agreed to co-develop and co-market SGLT2 inhibitor dapagliflozin (phase 3) in the future. This development seems in line with statements from company management – at the Morgan Stanley Global Healthcare Conference last year, BMS

President and COO Lamberto Andreotti highlighted plans to expand saxagliptin sales into the Asian-Pacific region.

- **Diamyd – Vaccine for type 1 diabetes (rhGAD65) granted orphan drug status by FDA:** The FDA has granted Diamyd Medical orphan drug status for Diamyd (rhGAD65), its proprietary treatment for type 1 diabetes with residual beta cell function. According to the Orphan Drug Act, a drug must be designed for a rare disease without current adequate treatment in order to gain Orphan Drug status. Drugs granted orphan status are given a seven-year period of market exclusivity in the US from the day of marketing approval by the FDA. Additional benefits usually include tax credits for clinical research, waiver of FDA user fees, study design assistance, and potentially even funding for clinical trials. Diamyd reported positive phase 2 trial follow up results in late 2009, and while detailed results were not reported, the company indicated that treated patients had "a clearly better diabetes status" compared to the placebo group at the four-year follow-up with no serious adverse events reported. A global phase 3 program (in nine European countries and a parallel study in the US) with the Diamyd vaccine is currently underway and aims to include 640 children and adolescents recently diagnosed with type 1 diabetes. As of September 1, 2009, the US-based trial will examine children ages 10-20, expanded from the initially designated limits of 16-20 years. The orphan drug designation is very good news for Diamyd and signals recognition on the part of the FDA that there is an important unmet need for the treatment and prevention of type 1 diabetes. We are looking forward to hearing more detailed discussion of data from the phase 2 and ongoing phase 3 trials, but current data suggests that the drug may be accessing a potential mechanism for beta cell protection—it may not be a cure, but it may be a step in the right direction. According to management, phase 3 trials will be completed in 2011 and the company plans to submit the drug to the FDA by 2012.
- **Novo Nordisk – Results of the LEAD-6 extension study of liraglutide published in Diabetes Care:** Dr. Buse and colleagues authored the results of the 14-week extension study to LEAD-6, in which patients in the exenatide 10 μg twice-daily arm were titrated to 1.8 mg liraglutide once-daily (Novo Nordisk's Victoza). This extension data was presented at ADA 2009 (following LEAD-6 data shown at the Canadian Diabetes meeting in 2008), but it has not been published in a scientific journal until last week. The Diabetes Care article largely contains the same data presented at ADA, although its publication will give the results some publicity that may encourage endocrinologists to switch Byetta patients to Victoza. All 389 patients completing the 26-week LEAD-6 study continued on to participate in the follow-up study: 187 from the exenatide group and 202 from the liraglutide group. Switchers showed a significant reduction in A1c from 7.2% to 6.9% over the 14-week follow-up period. Additionally, switching from exenatide to liraglutide increased the proportion of patients who achieved a glycemic target of <7.0%. Overall, 376/389 patients (97%) completed the extension. Six (3.2%) of the patients that switched from exenatide to liraglutide discontinued due to adverse events (mostly nausea), compared to zero in the liraglutide-continuers group. Notably, the higher dose of liraglutide (1.8 mg) was used instead of the 1.2 mg dose; the efficacy and adverse event data of 1.2 mg liraglutide is closer to the 10μg dose of exenatide, although there has not been a head-to-head study to demonstrate this finding. The 1.8 mg liraglutide dose is 50% more expensive than the 1.2 mg dose. Thus, in interpreting the results of this study, physicians and payors will have to weigh the additional financial costs with the potential glycemic benefits. Management did say that the co-pay for patients should be the same, regardless of dose (except, presumably, in plans that charge a patient a "share" of the total cost). Link to paper: http://care.diabetesjournals.org/content/early/2010/03/20/dc09-2260.abstract.
- **JDRF/Pfizer – Collaborate to advance Artificial Pancreas and beta cell regeneration research:** The JDRF will collaborate with a consortium of European academic and industrial

stakeholders working to advance the development of the artificial pancreas in Europe. The four-year project is called "AP@home" and will be coordinated by Lutz Heinemann, PhD (Profil Institut für Stoffwechselforschung GmbH, Neuss, Germany) and Hans DeVries (Academisch Medisch Centrum, Amsterdam, Netherlands). In the first phase of the project, the consortium will test current artificial pancreas algorithms with current CGM and insulin pump devices and work to improve the accuracy of the glucose sensors and improve the safety and efficacy of the algorithms. The consortium will also devote resources to developing an advanced combined insulin pump/CGM device that will only require one invasive catheter (patients are clapping wildly!). The final stage of the project will involve evaluating the efficacy of this new combined insulin pump/CGM advanced artificial pancreas in comparison to standard intensive insulin therapy in daily life in a multinational controlled trial. The JDRF also recently announced that it is partnering with academic and industry collaborators to advance the development of drugs for people with type 1 diabetes that can replicate and regenerate beta cells. The foundation and Pfizer will co-fund research at Hadassah Medical Organization directed by Benjamin Glaser, MD and at the Hebrew University in Jerusalem directed by Yuval Dor, PhD. Researchers at these two academic centers will perform preclinical exploration of up to three of Pfizer's proprietary compounds designed to promote beta cell replication and regeneration. We have seen the JDRF expand on its partnerships with smaller biotech companies a few years ago, and move into several new partnerships with larger businesses and even other patient advocacy organizations in the last year; we find the foundation's efforts to bring together academia and industry in synergistic ways commendable and innovative.

- **Merck – Januvia approved for distribution in China:** Merck's Januvia (sitagliptin) has been approved by China's State Food and Drug Administration (SFDA), allowing the company to bring its blockbuster DPP-4 inhibitor to a key emerging market with an estimated 43 million patients of diabetes, 70% of which are estimated to not be at goal. While Januvia will face increased competition in the US and Europe from more DPP-4 inhibitors and GLP-1 therapies entering the global market, it remains extremely easy to take and prescribe compared to other more traditional therapies. While reimbursement prospects for Januvia in China are not yet clear, a recent healthcare reform action plan in China will mandate coverage expansion to over 90% of the population (up from ~20% before reform) by 2011. China is expected to become the third largest pharmaceutical market by 2011. Currently the fifth largest market, China's impending health care reforms and major coverage expansion will translate into considerable growth in all health-care related markets. The Chinese government has committed to expanding coverage to over 90% of the population (up from ~20%) by 2011, with coverage of all 1.3 billion citizens by 2020. The government looks for rapid expansion in the next two years to be implemented through $124 billion spent on building 30,000 hospitals and over 4,000 clinics and health centers to service the 700,000 villages of China. Additionally, 1.37 million village and 160,000 community physicians will be trained. The plans are aggressive and companies well-positioned at the start could benefit enormously. For true success, drugs will need to end up on government-approved reimbursement lists—we hope to learn more about this reimbursement climate as the market takes more shape.

— by Sanjay Trehan, Eric Chang, Jessica Swienckowski, Nick Wilkie, and Kelly Close

4. DCU Interview: Dr. Lee Kaplan Discusses Therapies for Obesity

We recently had a fascinating discussion with obesity expert Dr. Lee Kaplan on the future of medical and surgical obesity therapies as well as hot topics in obesity research. An Associate Professor of Medicine at Harvard Medical School, Dr. Kaplan serves as the Director of the Weight Center at Massachusetts General Hospital in Boston, widely considered one of the leading obesity clinics in the world. Dr. Kaplan's clinical expertise is in the areas of obesity medicine, gastroenterology and liver disease. The author of more than 125 medical and scientific papers, he has a special interest in the causes and complications of obesity and the development of new and more effective preventive strategies and therapies for this problem. His clinical research is focused on identifying clinically relevant subtypes of obesity and exploring novel, combinatorial approaches to the treatment of obesity and its complications. Dr. Kaplan's basic research is focused on the physiological and molecular mechanisms of gastrointestinal regulation of body weight and metabolic function, and his group has pioneered the development and use of rodent models of weight loss surgery and gastrointestinal devices to explore these issues.

Dr. Kaplan is the Director of the Fellowship Program in Obesity Medicine and Nutrition at MGH, the first subspecialty training program of its kind; Associate Director of the NIH-sponsored Boston-area Obesity and Nutrition Research Center; a member of the NIH Clinical Obesity Research Panel; and Chairman of the Board of the Washington, DC-based Campaign to End Obesity. Dr. Kaplan graduated with honors from Harvard University. He received his MD and PhD in Molecular Biology, both with distinction, from the Albert Einstein College of Medicine.

Dr. Kaplan is a leading researcher in gastric bypass surgery and we were especially intrigued by his research on the physiological effects of bariatric surgery and his hopes to one day "bypass the bypass" – in other words, to mimic the physiological effects of surgery without the surgical procedure. As for pharmacotherapies, he expressed interest in substratifying patients with obesity and targeting small percentages of patients who exhibit outstanding responses to specific therapies, coining this the "Pacman approach." He singled out Vivus' Qnexa for its ability to induce an average weight loss of over 10% and characterized the efficacy of Arena's lorcaserin and Orexigen's contrave as being on par with sibutramine. Nevertheless, he is excited to have more products to prescribe in combination and hopes to "Pacman" away additional segments of the population as new agents with novel mechanisms of action reach the market. Notably, Dr. Kaplan believes improved efficacy will drive interest in obesity treatments more than simply improved side effect profiles.

Dr. Kaplan also discussed the mechanisms and risks associated with gastric bypass surgery, gastric banding, and the potential benefits of GI Dynamics' EndoBarrier and other devices. He provided a useful overview of the specific effects of surgical therapies that lead to resolution of diabetes and/or obesity, and he shared his thoughts on the growing acceptance of bariatric surgery. "Until about 10 years ago," he said, "bariatric surgery was really relegated to the backwaters of medical practice. Only in the last 10 years or so has it become clear that surgery provides extraordinary benefits for patients but that it also provides an exceptionally valuable model for understanding the physiology of energy balance and metabolic function. Studying these effects of surgery is likely to be one of the most direct means of identifying new and more effective non-surgical treatments of obesity and diabetes."

THE CURRENT AND FUTURE ENVIRONMENT FOR OBESITY THERAPIES

SANJAY TREHAN: There seems to be a variety of available therapies with limited efficacy and several side effects. Could you give us a broad overview of the current environment for obesity therapies? What do you think are the biggest challenges for patients with obesity?

DR. KAPLAN: I think the biggest challenge is that the drugs don't work well. If you subject medications to treat obesity to typical efficacy criteria, then they are all wanting; if you apply the less stringent efficacy criteria that we use for weight loss medications, then they work reasonably well. For example, with medications for hypertension or elevated cholesterol, the expectation is that they will bring blood pressure or cholesterol into the normal range. We don't want drugs that lower high blood pressure from 200/100 mmHg to 190/90 mmHg, because this degree of improvement would be obviously inadequate. Our expectation for most metabolic diseases is that medications will resolve the abnormalities. The problem with obesity is that there are no therapies that reliably bring someone into the normal range. So we are stuck with less complete resolution and less beneficial endpoints, such as several pounds of weight loss. On average, most drugs generate between 4% and 8% weight loss beyond what a placebo would give you. This degree of efficacy is statistically significant and can be clinically valuable, but it is ultimately unsatisfying for both patient and provider alike. If someone weighs 200 pounds and achieves 8% weight loss, that means they lose only 16 pounds, and even that amount of weight loss is usually not maintained.

So the end result is really limited efficacy of currently available medications, which is why they are not particularly successful in the marketplace. In terms of side effects, most of these drugs are pretty safe. Certainly, every drug has its risks, but the biggest challenge is that these medications aren't as effective as we would like them to be.

SANJAY: A related follow-up: when you say a drug that "is truly effective," are you referring to a particular threshold of weight loss?

DR. KAPLAN: There are published studies that have shown what most patients want in terms of weight loss. Ideally, of course, the drug would work 100%, meaning that the patient's weight would be normal after taking the drug for a period of time. I don't think that that outcome is anywhere within the range of possibility right now. More practically, I would like to see double-digit (10% or more) weight loss. Few, if any, of the medications now available or on the horizon will achieve this benchmark. Given their limited effectiveness for the total population of patients with obesity, I would prefer to take a different approach. It seems safe assume, based on clinical and epidemiological evidence, that there are multiple types of obesity, manifest by differences in the severity of obesity, age of onset, body fat distribution, comorbidities, and other symptoms (hunger, satiety, craving, etc). I would estimate that there are several dozen or as many as a hundred different subtypes of obesity, each of which is likely to respond differently to different therapies.

Therefore, rather than trying to reduce the weight of the entire population, which is highly unlikely to succeed because of the heterogeneity of patients with obesity, I would seek a therapy that has a more profound effect (e.g., causes full remission of obesity) in a small percentage of the population. If you have a therapy that can eliminate or fully control obesity in even 1% of patients, then that population can be taken out of the "at risk" pool. Additional therapies would then need to be developed for the other 99% of the population. With another therapy eliminating obesity in another 1%, we reduce the at risk group to 98% of original population, and so on. I think that given the heterogeneity of obesity, this strategy is more likely to be successful than one that requires a single agent or even a combination of agents to work, even modestly, in the entire population of people with obesity. No such agent has been developed previously, and I don't think it's a reasonable expectation, even with the tremendous advances in our understanding of the biology of weight regulation.

KELLY: So there would have to be personalized therapies or technologies?

DR. KAPLAN: Well, it wouldn't have to be personalized in advance because the beauty of a medication, as opposed to surgery, is that you can try it to see if it works. Even if only 1% of people respond dramatically to a particular drug, if that drug is safe, you could try it in nearly everyone with obesity. The 1% who respond are effectively taken out of the game because their obesity is resolved. For the other 99%,

the drug is stopped and you move on to try the next medication. If you have only one medication available, of course, this is not an effective strategy, but if you have 20 to choose from, you can experiment until you find the most effective medication or combination of drugs for each individual patient.

With more therapies available, we have more opportunities for success. We can try one or more drugs in sequence; depending upon the outcomes of these individual patient trials, we can then evaluate whether one or more combinations of drugs or other therapies might be more effective. So we'll then try various combinations in sequence. This is a highly empirical approach, and there is no magical way of doing it, but I believe it unlikely that a single drug is going to provide a large benefit to more than a small percentage of the population. The likelihood is that two or three-drug combinations will be much, much more effective. This approach makes sense and it's very attractive, especially when we look at the mechanisms of the one approach that does work -- surgery – and recognize that this intervention really embodies a combination of therapies within a single operation. I believe that the most important message from surgery is that to combat obesity successfully, we need to affect this very complex regulatory system at multiple points. At its core, bariatric surgery is a blunt tool that affects multiple nodes of this regulatory network. By contrast, most drugs are more selectively targeted and affect only one node of the network, which is inadequate to reverse the more widespread abnormalities in that network that cause obesity.

One way to think about this complex system is to imagine an orchestra of a thousand players (there are likely to be more than a thousand different genes involved in obesity) in which the players are out of tune with each other. It is unlikely that you will fix the problem by having a vigorous conversation with a couple of second cellos. You might need to retune several dozen or a hundred of the thousand instruments to bring the orchestra back in tune. On the other hand, in rare cases, you might be lucky enough that the only thing wrong with the orchestra is the second cellos and that targeted intervention would be enough. Retuning most orchestras, however, requires the broader intervention, and I think surgery provides that type of broad-based intervention for the physiological dysfunction that leads to obesity; it hits a lot of different parts of the relevant regulatory systems. But there will be that 1% of the population where the major cause of the obesity is directly in line with the effect of the drug, so for that 1%, the drug will be extraordinarily effective. If you take this more individualized approach, looking for the dramatic benefit in a small percentage of the population (what I call the "Pacman approach" to obesity therapy), then with enough different therapies, you can systematically control obesity in progressively larger subpopulations. Each time you "Pacman" away even a small subset of patients by providing truly effective therapy, you have made the kind of durable progress that allows focus on the next subset of patients.

DRUGS AND DEVICES IN DEVELOPMENT FOR OBESITY

SANJAY: Focusing on the drugs in development for obesity, what innovations are you most interested in? How important is to understand the mechanism by which these new drugs in development work?

DR. KAPLAN: Given our limited understanding, I am not certain that the mechanisms matter as much as whether or not the medication works. While my research is heavily focused on mechanisms of action, in the first instant what is most important is that the medication works (in at least a subpopulation of patients) and that it is safe for use in that population. If I had a choice of an effective and safe medication whose mechanism I didn't fully understand versus a less effective drug whose mechanism I fully understood, I (and most of my patients) would likely prefer the first one. Remember, of course, that most of the emerging medications don't work any better than the ones we already have. Their greatest opportunity will likely come either from their ability to effectively treat a new subpopulation of patients with obesity or from their ability to work as part of new, combination therapies. Among the emerging therapies, the one that does seem to work better than currently approved medications is Qnexa (Vivus),

which is a combination of phentermine and topiramate. This combination is commonly used in specialized obesity centers already, since both components are available as single agent. Indeed, generic forms of both topiramate and phentermine are available, which may turn out to be the most cost effective approach.

KELLY: Some of the doctors that we've spoken to have said that they can do that because they have a dietitian on staff, etc. but for the PCP, they may have a problem with the formulation and understanding exactly how to divide the pills.

DR. KAPLAN: I think there's merit in that view, but I think that we could educate primary care physicians in the use of this combination. There will likely be strong financial pressure to use the generic versions. The situation may be similar to BiDil, a combination of two generic medications that was shown to be particularly effective for treating heart failure in African Americans. In the end, the data from the BiDil development program for this proprietary combination proved its effectiveness for this subpopulation, but the drug itself was not successful because physicians primarily prescribed the combination of generic versions. My guess is that this is what may happen with Qnexa. Nonetheless, there is strong evidence that this combination is particularly effective. The effectiveness of the other emerging therapies such as lorcaserin (Arena) or the combination of naltrexone and bupropion (Orexigen's Contrave), appears to be similar to that of sibutramine. So while these medications may well be approved by the FDA, they will not solve the obesity problem. As a clinician, I would still like to see them approved. This is primarily because each of these agents provides a new therapeutic opportunity for a new subset of the population with obesity, and each one of them provides many new opportunities for potentially effective combinations. Lorcaserin has a mechanism of action that resembles fenfluramine but without the cardiac valvular effects. It is not as effective for treating obesity as fenfluramine but it resembles fenfluramine in its mechanism. The hope, as yet unproven, is that like fenfluramine, it could be combined with phentermine to generate a synergistic benefit. Many of us are eager for it to be approved so we can start conducting trials of lorcaserin-phentermine combination therapy. Will that combination be as effective as the old phen-fen combination? We don't know, but we're hopeful. But even if it's not effective in combination with phentermine and the benefit to the overall population of patients with obesity is limited, there is likely to be that 1% or 2% of the population that I keep referring to who appear to do well with each of the available drugs. We don't know why and we do not yet have a way of predicting who they will be, but if we have a patient who durably loses 50 or 60 pounds on any of these agents, that is one more patient whose obesity has been brought under better control. Both because each new agent provides additional opportunities for combination therapy and because each new drug with a new mechanism of action provides an opportunity to treat a new subpopulation of obesity more effectively, it will be valuable to have as many new drugs for obesity available to us as possible, providing of course that they are safe to use in the large number of people who are likely to be exposed to them.

KELLY: What do you think about the safety of these new drugs at the FDA, particularly Qnexa, since it has the first advisory panel?

DR. KAPLAN: There is a large school of thought that views obesity as a lifestyle choice, which is not a perspective that I share. Many people who have this perspective, however,, believe that any kind of medical therapy for obesity is inappropriate, whether it be surgical or pharmacological, because we typically don't treat lifestyle choices with medical therapy; we save such approaches for "disease." People don't always make this distinction consciously, but to the degree that it is considered inappropriate to use drugs, then virtually no drug would be viewed as safe enough. However, if you consider obesity as a real disease with real medical consequences, some measure of risk would be acceptable. In evaluating treatments for cancer, we commonly accept substantial risks of adverse effects. The question is where we place obesity among the spectrum of diseases. The answer to that question will determine what kind of risks you're willing to take in treating the obesity. We also must consider the wide heterogeneity of

obesity. While some forms of obesity may be potentially deadly, there's a broad distribution of manifestations. Nearly everyone wants to lose some weight at some point in their life. So there is always a risk that people who have no medical indication will take a particular weight loss drug. This consideration needs to be taken into account when looking at the risks (and benefits) of any particular medication. But the notion that drugs for obesity should be risk-free stems from the perspective that obesity is not worth treating medically at all. If a disease is risky enough to require treatment, it is risky enough to accept some measure of risk from the therapy. The critical factor is the relative risk vs. benefit of the therapy in individual patients.

SANJAY: We've heard you speak at various meetings on GI Dynamics' EndoBarrier, which sounds like a very innovative approach. Has this device taught us anything from a mechanistic point of view about the effects of surgery on obesity and diabetes?

DR. KAPLAN: This device appears to reproduce one or two of the mechanisms of bypass surgery. I like to conceive of bypass surgery as five operations in one: the isolation of the small part of the stomach, exclusion of the remainder of the stomach, exclusion of the proximal small bowel, exposure of the mid and distal small bowel to undigested nutrients, and a partial vagotomy. Of these five components, only two are reproduced by this device. This device appears to have a profound beneficial effect on diabetes, both in animal models and in early human data. It has a more modest effect on obesity. We can infer from these observations that the intestinal part of the gastric bypass has a greater impact on diabetes. And through other studies, including studies of gastric banding, we can say that the stomach part of the bypass seems to have a greater effect on diminishing food intake. From a clinical perspective, the fact that the EndoBarrier seems to have many of the same effects on diabetes as a gastric bypass is very powerful because this device is a lot less invasive than a bypass.

The device, however, also has its limitations. In its current form, it is not a permanent solution, unlike a bypass, which is permanent. But to have a substantially less invasive approach that accomplishes the same physiology as the bypass, at least with respect to diabetes, makes this a very attractive approach. One of the goals of our research on how surgery works is ultimately to "bypass the bypass." We hope to discover a less invasive method of achieving the same benefits as a bypass. One way to do this might be with combinations of medications; another way could be to use devices that reproduce all or part of the effects of surgery. The EndoBarrier seems to be a very attractive device for that purpose.

KELLY: Do you think people who aren't obese, but slightly overweight, will try to use this device?

DR. KAPLAN: There are several studies going on around the world aiming to determine whether people with type 2 diabetes without obesity or with only mild obesity would benefit from gastric bypass surgery. While surgery appears to provide clear benefit for the management of diabetes, the risk of the surgery in this lower weight population is less clear. We don't know how the risk-benefit relationship will play out in this population. I would argue that there are probably going to be some subgroups of patients, who are relatively thin, who have diabetes, are not well controlled with drugs, and for whom surgery is the right answer, even though they don't have obesity. If this is true, then it will be very attractive to have a less invasive approach with the same effects on diabetes as bypass surgery. I think that the problem with the EndoBarrier device is that it is not permanent. Of course, it may not need to be permanent if it can stay around for a year or two and then can be taken out and a new one can be implanted a few months later. Since it is placed endoscopically in 20 or 30 minutes, the barriers to repeated implantation are much lower. There are many reasons for periodic endoscopies, so the notion of doing an endoscopy once a year or every two or three years to replace the device is not prohibitive in terms of risks or inconvenience to the patient. If we can do that, then maybe the EndoBarrier can provide a long-term solution even though the device itself is not permanent. This approach, if doable, would be very attractive because the overall risk would be presumably much lower than the risk of gastric bypass or banding.

KELLY: Dr. Kaplan, thank you so much for all of your generosity – we're so excited to be able to share your thoughts with our readers.

SANJAY: Thank you, Dr. Kaplan!

— by Sanjay Trehan and Kelly Close

5. Conference Pearls: 6th Annual Clinical Diabetes Technology Meeting

April 9-10, 2010 • San Antonio, TX • http://www.clinicaldiabetestechnology.org/

We are pleased to present you with select highlights from the 2010 sixth annual Clinical Diabetes Technology Meeting, held this year on the historic River Walk of San Antonio, Texas. The engaging speakers presented to a mix of nearly 300 healthcare professionals and others; nurses/educators comprised 34% of the audience, members of industry represented nearly one third of the audience, 26% were physicians, and 8% were dieticians. There were several insightful discussions, led by some of the most impressive names in the field (Drs. Bruce Buckingham, Barry Ginsberg, William Clarke, Robert Gabbay, and Zachary Bloomgarden, to name a few) on topics ranging from SMBG accuracy, CGM, and insulin pump use in the hospital, to tight glycemic control in the intensive care unit. Below we present key highlights from this always informative meeting including pertinent selections from the five-person hour-long patient panel featured at the meeting-- patients discussed how they used their CGM devices, what they liked, what they didn't like, and what they hope to see in future generations.

- **Bruce Buckingham, MD (Stanford University, Stanford, California), one of the most experienced CGM authorities in the field, discussed the benefits and limitations of this technology for managing diabetes.** At the beginning of his talk, a quick poll of the audience revealed that 35% do not use CGM in their practice, and 25% have 1-10 patients using CGM and 21% have over 30 patients using CGM (the other 19% were scattered between 10-30 patients using CGM). Interestingly, 58% of the audience believed that the greatest barrier to starting CGM is insurance reimbursement and another 19% believe that there is insufficient reimbursement for HCP effort in initiating CGM. Before discussing the technical aspects of "getting started with CGM", Dr. Buckingham masterfully covered volumes of data showing the accuracy, safety, and efficacy of the sensors. He took time to again note his disappointment that there is not a low-glucose suspend sensor-integrated pump available in the US at this time, noting that that no one has died from two hours of suspended pump therapy but many patients die every year from nocturnal hypoglycemia (echoing his comments at the recent ATTD meeting in Basel February 2010). In discussing more practical aspects of CGM use, Dr. Buckingham gave tips on performing the first calibration, how to use the rate of change arrows and alarms, and how to deal with special considerations for certain CGM users (such as athletes). He concluded by discussing appropriate candidates for CGM and strongly emphasizing that both HCP and patient expectations need to be realistic in order to gain the most out of CGM.
- **Barry Ginsberg, MD, PhD (Diabetes Technology Consultants, Wyckoff, New Jersey) reviewed the inaccuracy, "necessary accuracy," and sources of error in self-monitoring of blood glucose (SMBG).** Although this was the most detailed talk we have ever heard on the topic, and one from which we learned a great deal, we were disappointed by Dr. Ginsberg's recommendation that meters should be available in several different accuracy ranges. From our view, it would be simpler for patients and practitioners to have an updated accuracy requirement for all patients. Dr. Ginsberg helpfully discussed various factors affecting the accuracy of SMBG, including strip factors (strip-to-strip variation, stability), physical factors

(temperature, altitude), patient factors (coding, hematocrit, technique, hand washing), and pharmacologic factors (medications, dialysis fluid). While according to Dr. Ginsberg, different patients require different levels of minimal accuracy, the evidence for SMBG in type 2 diabetes patients on non-hypoglycemic agents (non SFU, non insulin) remains unclear. Nevertheless, several technologies are being developed to improve the accuracy of blood glucose meters, including AC impedance, dynamic electrochemistry, and multiple electrodes. Finally, Dr. Ginsberg recommended external clinical testing of random lots of meters to guarantee a level playing field and standardized analysis and labeling of all meters on the market. Notably, in his talk, Dr. Ginsberg estimated that the average error in selecting a final insulin dose is roughly 27% and error from blood glucose meters is relatively minor compared to other errors. He was especially in favor of labeling the accuracy of blood glucose meters; while we agree that increased accuracy of meters may not be necessary for non-insulin treated type 2 diabetes patients, we recommend every patient has access to the same meters at the same prices – there would be too much confusion and/or complexity in our view for different accuracy SKUs, etc. We also believe patients should not be required to pay any higher fees to cover the meters.

    - Notably, Dr. Ginsberg believes meter accuracy is most important in type 1 diabetes patients, who use these data for insulin dosing, hypoglycemia detection and calibrating continuous glucose monitors (CGM)—we would point out that this is true for at least as many type 2 patients on insulin as all type 1 patients (about 4-5 million type 2 patients in the US alone are on insulin with some of these on MDI – likely more than ~1.5 million type 1 patients). While the 1993 ADA consensus recommendation calls for ±5% accuracy, Dr. Ginsberg recommended ±5-10% for type 1 diabetes patients. We note that although the ADA did call in the mid 1990s for 5% accuracy, we think the new standard is not at all likely to move to that at present and that this goal was aspirational if anything – we don't think the ADA actually believed that industry would move close to this.

- **William Clarke, MD (University of Virginia Medical Center, Charlottesville, Virginia) delivered a discussion on clinical accuracy of blood glucose monitoring.** He began by exploring how clinical accuracy is different from statistical accuracy and how the two interact. While ISO criteria is the gold standard for statistical accuracy, Dr. Clarke believes these criteria are not appropriate for evaluating clinical accuracy—where error grid analysis is the preferred tool. He went on to note that different error grids exist than the one he and his colleagues created (such as the Parkes consensus error grid) and that error grid analysis can even vary for different patient populations (i.e., type 1 patients v. type 2 patients). Dr. Clarke walked the audience through a fascinating exercise showing how the error grid changes when target ranges are altered for different patient populations (such as in the ICU and in pregnant women). He said the target range of 80-110 mg/dl in the ICU (we aren't sure which hospitals still have this as a target) results in a marked increase in Zone C error; this increases the likelihood of overtreatment and the risk of hypoglycemia – we had not heard this before and certainly are interested in discussing this with experts in this area. Clinical accuracy is also affected by limitations such as the frequency and timing of blood glucose testing and the interpretation of results. Dr. Clarke emphasized that we must remember that insulin dosing has its own error as well (especially if delivered through syringes), and ultimate therapy accuracy will be compounded by both SMBG error and dosing error—this compounded error could be very serious for patients sensitive to insulin. Notably, near the conclusion of his talk, Dr. Clarke endorsed CGM, noting that the information it provides can be more helpful for clinical decisions than point estimates provided by blood glucose meters. Dr. Clarke also implied that believes one test per hour is completely insufficient in the hospital considering the rate that insulin acts in IV infusion (10 minute half-life).

- **Robert Gabbay, MD, PhD (Pennsylvania State University, Hershey, Pennsylvania) tackled a topic that has been of enormous interest in the past year—diabetes drug safety in type 2 diabetes.** After giving a brief overview of the new (2008) FDA cardiovascular (CV) risk assessment requirements, he went on to review several specific drugs, commenting on safety concerns that have arisen. In his discussion on sulfonylureas, he highlighted concerns about hypoglycemia and weight gain, and focused on CV concerns that plagued older versions of the drug but do not appear to be an issue with newer sulfonylureas. Moving on to metformin, Dr. Gabbay covered the CV benefits associated with metformin (a 39% reduction in myocardial infarction in UKPDS) and recent data suggesting there should not be concern over congestive heart failure or lactic acidosis. On TZDs, Dr. Gabbay discussed class-wide concerns such as fluid retention, congestive heart failure, and osteoporosis, before moving on to agent-specific concerns surrounding rosiglitazone (GSK's Avandia). GLP-1s, once believed to be relatively side effect free, have recently raised concern over pancreatitis and safety problems in patients with renal insufficiency. Another major concern with these drugs (at first believed to be exclusive to liraglutide but has not been ruled out as a class-effect) is the c-cell carcinomas observed in rodents, but this issue has not yet been observed in humans. In closing, Dr. Gabbay turned to the well-known cancer scare with insulin in type 2 patients, originating from a set of retrospective studies published in Diabetologia in late 2009. After discussing these concerns and methodological problems with the retrospective studies, he emphasized that most large randomized controlled trials do not support an increased risk for cancer with the use of insulin. A poll of the audience revealed they are most concerned about the safety of rosiglitazone and the TZD class in general, and have the lowest concern over the incretin class.

Excerpts from the Patient Panel—Personal Experiences with Real-Time Continuous Glucose Monitoring:

Q: How accurate do you find the CGM and do you find the alarms a nuisance?

Robert: I kept records for an entire year and I found that mine was inaccurate 47% of the time and it is usually ±20 mg/dl of my meter if not more.

Evelyn: Its not as accurate compared to finger pricks, that's why I test myself about 8-10 times a day still. I do not rely entirely on my CGM. I will actually often use two meters for my finger pricks, because they are not always accurate either.

Debbie: Much to my dismay I have found recently that it is not that accurate. I have had problems with it being 50-100 points off. I prick my finger often. It needs to be used as a guide and not a bible. You honestly cannot use your meter as a bible either.

Barbara: I usually find a less than 10% difference between my DexCom and the finger prick. When I was on Medtronic I actually had a lot of problems. My Medtronic would say I was at 200 mg/dl and my blood sugar was actually 75 mg/dl. When DexCom came out it was recommended to me and I found that it was much more accurate and I am much more comfortable. It is not worth my time to invest in something that is going to be off so much.

Marin: When I put my new DexCom sensor on, the first two to three days it might be a little bit off. But every time I prick my finger I just calibrate it because it is not that hard to just punch in the number when you get the reading. By the third day it is nearly perfect, definitely within 10%. I know this is not recommended, but if I want to try to get another week or sometimes even more out of a sensor, I will sometimes just restart the system and use the same sensor. I have found that when I do this, typically, the first day when I restart that sensor it will be spot on and it will be great until the sensor fails.

Q: What are your favorite features about your CGM?

Maureen: I look at the up and down arrows to project when my blood sugar is going low. One thing with the CGM is that I don't think I would ever be in a diabetic coma since it would continuously go off every 5 minutes before that could happen. I'd much rather hear those alarms than end up on my floor when no one is around me.

Evelyn: I like the numbers and I like the arrows also. Initially, I liked the alarm, especially when I'm at work. Even the surgeons will tell me, "OK Evelyn, check your sugar" when it beeps. But I hate the alarm in the middle of the night. You will be fast asleep and there will be this alarm. That is why I try to get my sugar just right before I go to bed and then I just turn my alarm off. (Editor's note – we can't imagine this is advocated by her healthcare team.)

Debbie: I like it. I like the arrows and alarms although it isn't as accurate as I would like it to be. It definitely wakes me up to prevent me from going too low and I like that.

Barbara: I like that I don't have to check every five minutes whenever I feel strange, which I might feel for some other reason, like a stressful day at work.

Marin: I appreciate the new model of DexCom, which lets me see a three-hour graph at the push of a button. I really do like the trend graph more than the arrows.

Q: What would you like to see in a next generation CGM, your wish list?

Robert: I'd like to see it be more accurate so I didn't need to do 14 fingersticks every day. That would be the greatest thing, for it to be reliable.

Maureen: I don't like the 10-hour delay from when you put it on and to get your first reading. I would only like the alarm to wake me up at night if I am dropping below 60 mg/dl. Sometimes I have a bit of trouble keeping the device on for five days but there are different takes on that after talking to the rest of the panel.

Evelyn: I wish that the monitor would measure the blood sugar and not the interstitial fluid so it would be more accurate. I would also like to see a smaller version so we can wear nice clothes without any bumps.

Debbie: I'd like to see the accuracy change. I understand others have better accuracy and can wear it for a longer period of time. With the MiniMed, you can only wear it for three to four days. I found a better tape as well – it was always coming off in this hot San Antonio weather. I would also like to see a multiple alarm setting, where you can set different settings at night than during the day because it keeps me up.

Barbara: I would like to see the DexCom integrated into my pump. When I was on the MiniMed, it was integrated. I'm very comfortable with using my sensor but I would also just like it to be smaller. And whoever designed the cases they have must not have been looking at it because it looks very awkward—please have a decent case that works.

Marin: On the transmitter side, you can fix the tape but at that seven-day mark, it doesn't look very pretty. Aesthetically, you want it to not look so dingy. The receiver is kind of thick as well, probably 3/4 inch and an odd shape as well so I am always looking for places to hide it. I am called the bionic woman at work because I have the receiver and the pump and I'm always pulling things out, so anything smaller would be nicer. For me, the receiver could have a glucose meter built in it as well so it would calibrate it immediately.

— by Jessica Swienckowski and Sanjay Trehan

6. Conference Pearls: 59th Annual Scientific Sessions of the American College of Cardiology

In March, we attended the 59th American Cardiology Conference, held in the massive Georgia World Congress Convention Center. With over 33,000 (!) registered participants, nearly every session we attended was overcrowded with people inside and outside of the conference room. On the first day, we heard the much-anticipated results of the ACCORD lipid and blood pressure studies. In addition, we heard Dr. Rury Holman and Dr. Robert Califf present the results of the NAVIGATOR study, which evaluated the effect of valsartan and nateglinide (Novartis' Starlix) on the incidence of diabetes and cardiovascular outcomes (for more information on the valsartan arm of the study, see the Literature Review section). After the late-breaking clinical trial session, we had the opportunity to attend a roundtable discussion on the NAVIGATOR study. The roundtable discussion consisted of a table of 10 people, including the lead investigators – interestingly, the roundtable for the NAVIGATOR trial attracted the most attention, by far, with over 30 people hunched over the table as Dr. Robert Califf and Dr. John McMurray discussed the intricacies of the study's design and results. While these studies did not show a significant reduction in the primary endpoint of cardiovascular outcomes, we hope they will continue to build the knowledge base and push the field forward. We also gained valuable insight into the cardiologist's perspective of treating obesity and diabetes – almost every assertion or opinion was supported with a study on cardiovascular events/outcomes! Notably, Dr. Darren McGuire reviewed the results of various diabetes trials in a talk titled "Glycemic Control: How Tight should it be?" and provided an informative table of planned cardiovascular outcomes trials for diabetes drugs.

- **William Cushman, MD, FACP, FAHA (University of Tennessee Health Science Center, Memphis, TN) discussed the results of the ACCORD blood pressure trial in patients with type 2 diabetes.** The ACCORD blood pressure trial was a nonblinded study that randomized 4,733 patients to received either intensive blood pressure therapy (target of SBP <120 mm Hg; n=2,362) or standard blood pressure therapy (target of SBP <140 mm Hg; n=2,371). Patients were required to have stable type 2 diabetes for at least three months and an A1c of >7.5%. At baseline, patients were 62 years old, on average, and had a mean BMI of 32.1 kg/m2, A1c of 8.3%, and blood pressure of 139 mm Hg/76 mm Hg (87% were antihypertensive and 34% had cardiovascular disease). The intensive intervention began with two-drug therapy, involving a thiazide-type diuretic in combination with an ACE inhibitor, ARB, or a beta-blocker. Drugs were then added/titrated at monthly visits to achieve an SBP of <120 mm Hg. In the standard intervention group, therapy was intensified if SBP was ≥160 mm Hg at one visit or ≥140 mm Hg at two consecutive visits. Conversely, drugs were down-titrated if SBP was <130 mm Hg at one visit or <135 mm Hg at two consecutive visits. Similar to the ACCORD lipid trial, the primary outcome measure of the study was the first occurrence of a major cardiovascular event (nonfatal myocardial infarction, nonfatal stroke, or cardiovascular death).

  After 16 months of treatment, the mean systolic blood pressure (SBP) was 119.3 mm Hg in the intensive therapy group and 133.5 mm Hg in the standard-therapy group and the mean diastolic blood pressure was 64.4 mm Hg in the intensive group and 70.5 mm Hg in the standard group. Not surprisingly, the lower blood pressure observed in the intensive therapy arm was associated with a higher number of medications prescribed (this occurred across all drug classes), with 3.4 medications prescribed, on average, in the intensive therapy arm and 2.1 medications in the standard therapy arm. As expected, the intensively treated group experienced significantly higher rates of serious adverse events (hypotension and bradycardia/arrhythmia) as well as significantly higher rates of hypokalemia (potassium <3.2 mmol/l), elevations in serum creatinine (>1.5 mg/dl in men; >1.3 mg/dl in women), estimated glomerular filtration rate (eGFR; <30/ml/min/1.73 m^2). Finally, there was no significant difference in the primary outcome between the intensive and

standard treatment groups. Any stroke and nonfatal stroke were significantly reduced in the treatment group. Nevertheless, the number of major coronary disease events was much greater than the number of total strokes; therefore, as Dr. Peter Nilsson, MD, PhD (University Hospital, Malmo, Sweden) concluded in an NEJM editorial published this morning, "the main conclusion to draw from this study must be that a systolic blood pressure target below 120 mm Hg in patients with type 2 diabetes is not justified by the evidence."

- **Henry Ginsberg, MD (Irving Institute for Clinical and Translational Research, New York, NY) presented the much anticipated results of the ACCORD lipid study, which evaluated the effect of combination lipid therapy on cardiovascular events in type 2 diabetes.** The ACCORD study randomly assigned patients to receive either intensive glycemic therapy or standard therapy. The ACCORD lipid study recruited a subgroup of patients (n=5,518) with type 2 diabetes (A1c ≥7.5%) and randomized them in a 2x2 factorial design, to receive simvastatin in combination with a fenofibrate (n=2,765) or placebo (n=2,753). Patients were eligible to participate if they had an LDL cholesterol level of 60-180 mg/dl (1.55-4.65 mmol/l), an HDL cholesterol level below 55 mg/dl (1.42 mmol/l) if female or African-American and below 50 mg/dl (1.29 mmol/l) for other groups, and a triglyceride level below 750 mg/dl (8.5 mmol/l) if not on lipid therapy (400 mg/dl if receiving lipid therapy). Baseline characteristics between the two treatment groups were very similar: mean age was 62 years, 31% of patients were female, roughly 60% of patients were taking a statin, and 37% had a previous cardiovascular event. Baseline mean LDL was 100.5 mg/dl (2.6 mmol/l), HDL was 38.1 mg/dl (0.99 mmol/l), and triglycerides were 187.6 mg/dl (4.9 mmol/l). The primary outcome of the study was the first occurrence of a major cardiovascular event, which includes nonfatal myocardial infarction, nonfatal stroke, or death from cardiovascular causes. The mean duration of follow-up was 4.7 years for the primary outcome.

- **Rury Holman, MD, ChB, FRCP (Oxford Center for Diabetes, Oxford, UK) presented data from the NAVIGATOR study on the effects of nateglinide (Novartis' Starlix) on the incidence of diabetes and cardiovascular events.** The NAVIGATOR study aimed to determine the effects of valsartan and nateglinide, in a 2x2 factorial design, on the incidence of diabetes and cardiovascular outcomes over a five-year period. As a reminder, nateglinide is an oral antidiabetic agent of the meglitinide class, with a mechanism of action similar to that of sulfonylureas. Patients were eligible to participate in the study if they had impaired glucose tolerance, a fasting plasma glucose (FPG) of ≥95 mg/dl and <126 mg/dl, and either cardiovascular disease (in patients at least 50 years of age) or at least one cardiovascular risk factor (in patients at least 50 years of age). At baseline, patients were 64 years of age and obese (average BMI of 31 kg/m2), with an A1c of 5.8%, a FPG of 110 mg/dl (6.1 mmol/l), and a high rate of cardiovascular risk factors (for example, 77% of participants had hypertension). The study randomized 9,306 individuals to receive either nateglinide (with or without valsartan; n=4,645) or placebo (with or without valsartan; n=4,661). There were three primary outcomes: incidence of diabetes, extended composite cardiovascular outcome (death from cardiovascular cause, nonfatal MI, nonfatal stroke, hospitalization for heart failure, arterial revascularization, or hospitalization for unstable angina), and a coprimary core cardiovascular outcome (death from cardiovascular cause, nonfatal MI, nonfatal stroke, or hospitalization for heart failure).

  All patients in the study were required to participate in a lifestyle modification program designed to reduce the risk of diabetes by encouraging physical activity and a healthy diet. Patients assigned to the nateglinide group received a dose of 60 mg to be taken before meals three times daily (note – high hassle factor associated with 3x daily dosing). Although nateglinide caused statistically significant reductions in the fasting plasma glucose of 0.47 mg/dl (0.03 mmol/l; p=0.03), glucose levels after a two-hour post-glucose challenge were statistically significantly

higher in the nateglinide group compared to the placebo group, with a mean difference of 4.37 mg/dl (0.24 mmol/l; p<0.001). This was an unexpected result and Dr. Holman provided two possible explanations for this finding: 1) patients did not take the morning dose of nateglinide prior to the oral glucose tolerance tests and, therefore, the results may reflect a rebound effect of not having any drug-on- board; or 2) it may reflect beta-cell exhaustion/burnout, a long-term effect of insulin secretagogues. Unfortunately, there is no data to support either theory. While the goal of this study was to determine the effect of reducing postprandial hyperglycemia in preventing diabetes and reducing cardiovascular outcomes, the study failed to effectively lower postprandial hyperglycemia in patients with impaired glucose tolerance. In addition, nateglinide nearly doubled the incidence of hypoglycemia, an expected (and quite negative) side effect of meglitinides; we found this interesting, given that it did not sufficiently reduce postprandial hyperglycemia. Finally, there were no significant differences in any of the primary outcome measures between the nateglinide group and the placebo group; in fact, the hazard ratio favored the placebo group for the incidence of diabetes and death from cardiovascular causes. Overall, this was quite a negative result for nateglinides; since the drug already has problems associated with adherence, we don't believe it currently receives significant marketing support.

- **Darren McGuire, MD, MHSc, FACC, FAHA (University of Texas Southwestern Medical Center, Dallas, TX) reviewed the risk of cardiovascular disease in diabetes.** While he focused strongly on the UKPDS study in his previous presentation, he briefly reviewed the design and results of the ACCORD, ADVANCE, and VADT studies in this session. He concluded that no clinically important or statistically significant differences in outcomes were observed in these trials. Although these studies have largely been interpreted as negative, he believes they are neutral and suggest that the level of glycemic control currently being targeted by physicians is likely adequate and lowering glucose any further is "not necessary." Dr. McGuire also referenced the PROactive study, which showed that pioglitazone (Takeda's Actos) significantly reduced cardiovascular outcomes in high-risk diabetes patients. As a reminder, there was a 16% reduction in the main secondary endpoint of all-cause mortality, nonfatal MI, and stroke with pioglitazone relative to placebo (HR=0.84; p=0.027). In general, Dr. McGuire believes that the role of glucose control in cardiovascular risk mitigation remains uncertain; however, there is strong evidence of cardiovascular benefit from global risk reduction (including cholesterol control, blood pressure control, etc.), especially in diabetes patients. Lastly, we have provided the complete table of cardiovascular outcomes trials that Dr. McGuire displayed in both of his presentations – he specifically highlighted aleglitazar and canagliflozin as two novel classes of drugs, PPAR modulators and SGLT2 inhibitors:

Trial Name	Diabetes Drug	Estimated Enrollment	Initiation Date
ORIGIN	Insulin glargine (sanofi-aventis' Lantus)	12,500	09/2003
TECOS	Sitagliptin (Merck's Januvia)	14,000	12/2008
ACE	Acarbose (Bayer's Precose)	7,500	02/2009
TIDE	Rosiglitazone (GSK's Avandia) versus pioglitazone (Takeda's Actos)	16,000	05/2009
EXAMINE	Alogliptin (Takeda)	5,400	09/2009
CANVAS	Canagliflozin (J&J)	4,500	11/2009
T-emerge 8	Taspoglutide (Roche)	2,000	01/2010
AleCardio	Aleglitazar (Roche)	6,000	02/2010
SAVOR TIMI-53	Saxagliptin (BMS/AZ's Onglyza)	12,000	03/2010

EXSCEL	Bydureon (Amylin's EQW)	12,000	Not initiated
LEADER	Liraglutide (Novo Nordisk's Victoza)	9,000	Not initiated

- **Danielle Duffy, MD, FACC (Thomas Jefferson University Hospital, Philadelphia, PA) discussed the most recent guidelines and goals for lipid control in people with diabetes.** Of all the lipoproteins, LDL-C remains the most important for cardiovascular risk reduction, mainly due to data demonstrating that each 30 mg/dl increase in LDL cholesterol translates into a 30% increase in relative risk for coronary heart disease (NCEP ATP III: Grundy et al., Circulation 2004). In addition to LDL, other important parameters include non-HDL cholesterol (a measure of ApoB containing lipoproteins), ApoB (which may be a better predictor in patients already on statin therapy), and LDL particle number (not included in the current guidelines because of a lack of widespread availability and relative expense, according to Dr. Duffy). She also noted that diabetes patients often have atherogenic dyslipidemia characterized by high triglycerides, low HDL levels, and small LDL size. The recently published ADA 2010 guidelines suggest categorizing patients as either "high risk" or "highest risk." For achieving LDL goals, statins remain first-line therapy; the new guidelines support the use of statins regardless of baseline lipid levels for the highest risk diabetes patients, especially those >40 years of age. Although a recent meta analysis of 13 trials demonstrated a 9% increase in incident diabetes following the use of statins (Sattar et al., Lancet 2010), Dr. Duffy this in perspective by stating that 255 patients would need to be treated with statins for four years to observe one additional case of diabetes. Therefore, the overall absolute risk of developing diabetes is low. The authors of the study performed a subgroup analysis, which showed that the increase in incident diabetes did not occur in patients <60 years of age, leading them to conclude that clinical practice should not change based on these results. Lastly, Dr. Duffy suggested the use of various therapies for related comorbidites, including residual LDL-C elevation (bile acid sequestrants, ezetamibe, niacin), atherogenic dyslipidemia (niacin), and elevated triglycerides (fibrates, omega-3 fatty acids) – while no outcomes data currently exist for ezetamibe and niacin, we eagerly await the results of IMPROVE-IT and the Heart Protection Study 2 for more data on each of these drugs, respectively.

— by Sanjay Trehan

7. Literature Review: The Effect of Valsartan on the Incidence of Diabetes and Cardiovascular Events

The NAVIGATOR Study Group. *New England Journal of Medicine*, March 2010, 362 (18): 1748.
http://content.nejm.org/cgi/content/full/NEJMoa1001122

The NAVIGATOR study aimed to determine the effects of valsartan and nateglinide, in a 2x2 factorial design, on the incidence of diabetes and cardiovascular outcomes over a five-year period. As a reminder, valsartan is an angiotensin II receptor agonist, currently marketed by Novartis under the brand name Diovan in the US. The study design and primary outcomes of the NAVIGATOR trial were identical to those described for the nateglinide substudy. The study randomized 9,306 individuals to receive either valsartan (with or without nateglinide; n=4,631) or placebo (with or without nateglinide; n=4,675). There were three primary outcomes: incidence of diabetes, extended composite cardiovascular outcome (death from cardiovascular cause, nonfatal MI, nonfatal stroke, hospitalization for heart failure, arterial revascularization, or hospitalization for unstable angina), and a coprimary core cardiovascular outcome (death from cardiovascular cause, nonfatal MI, nonfatal stroke, or hospitalization for heart failure). Valsartan treatment significantly reduced the progression to diabetes

by 13% (HR=0.86; p<0.001). Interestingly, the valsartan group did not achieve a significant reduction in the primary cardiovascular outcome. Finally, we have included highlights from a roundtable discussion with the lead investigator of the valsartan substudy, conducted at this year's American College of Cardiology conference, where the results of this trial were initially presented.

- **Patients were eligible to participate in the study if they had impaired glucose tolerance and an elevated fasting plasma glucose (FPGs).** Elevated FPG was defined as ≥95 mg/dl and <126 mg/dl. In addition, patients were required to have either cardiovascular disease (in those at least 50 years of age) or at least one cardiovascular risk factor (in patients at least 55 years of age).
- **Participants were randomly assigned to valsartan 160 mg once daily or placebo (due to the 2x2 factorial design, a subset of each arm consisted of patients on nateglinide).** Patients initially received valsartan 80 mg; the dose was increased to 160 mg after two weeks. In addition, all patients in the study were required to participate in a lifestyle modification program designed to reduce the risk of diabetes by encouraging physical activity and a healthy diet.
- **The study randomized 9,306 individuals to receive either valsartan (with or without nateglinide; n=4,631) or placebo (with or without nateglinide; n=4,675).** Baseline characteristics were largely similar between the two arms of the study. On average, patients were 64 years of age with an A1c of 5.8%, a BMI of 30.5 kg/m^2, blood pressure of 140/83 mm Hg, HDL of 50 mg/dl, and LDL of 126.5 mg/dl. Roughly 24% of patients had a history of cardiovascular disease and 77% of patients had hypertension. At baseline, approximately 37% of patients were on aspirin or another antiplatelet drug, 39% were on a beta-blocker, 32% were on a calcium-channel blocker, 32% were on a diuretic, 39% were on a lipid-modulating drug, and <1% were on an antidiabetic drug. There were no statistically significant differences between the two arms of the study. While there was no significant difference at baseline, it is important to note that at the last study visit, a significantly higher proportion of patients in the placebo group were on an ACE inhibitor, an angiotensin-receptor blocker, an alpha-blocker, a calcium-channel blocker, a diuretic, any antihypertensive drug, or any antidiabetic drug.
- **The median follow-up time on the diabetes, extended CV, and core CV outcomes data were 5.0, 6.3, and 6.4 years, respectively.** Roughly 13% of participants in both the valsartan group (n=588) and the placebo group (n=623) were either lost to follow-up or withdrew from the study.
- **Valsartan treatment significantly reduced the progression to diabetes by 13% (HR=0.86; p<0.001).** The cumulative incidence of diabetes was 33.1% in participants treated with valsartan, compared to 36.8% in those treated with placebo. The fasting plasma glucose (FPG) decreased by 0.59 mg/dl (0.03 mmol/l) in the valsartan group compared to the placebo group (p <0.01). Glucose levels after a two-hour glucose challenge were also significantly reduced by 3.15 mg/dl (0.18 mmol/l) in the valsartan group compared to the placebo group (p <0.001). However, to determine whether valsartan truly prevented the development of diabetes, follow-up studies tracking FPG and oral glucose tolerance must be conducted after patients cease treatment for a period of time. In addition, significant reductions were observed in systolic blood pressure (2.8 mmHg; p<0.001) and diastolic blood pressure (1.4 mmHg; p<0.001)
- **Valsartan did not significantly reduce the incidence of the core cardiovascular outcome (14.5% in the valsartan group, as compared to 14.8% in the placebo group; p=0.43), or the extended cardiovascular outcome (8.1% vs. 8.1%; p=0.85).** However, this may be explained by the 13% loss to follow-up or the significantly increased use of

angiotensin II receptor blockers (ARBs) and ACE inhibitors in the placebo population at the last study visit (24.4% of the placebo population, compared to 20.8% in the valsartan-treated population). None of the individual component outcomes were significantly different between the two groups.

- **During a roundtable discussion at the 2010 American Cardiology Conference, lead investigator Dr. John McMurray, MD (University of Glasgow, Scotland, UK) reviewed several theories that connect valsartan to the development of diabetes**; for example, valsartan and other renin-angiotensin system (RAS) blockers increase skeletal muscle blood flow, which may be involved in regulating blood glucose levels and improving insulin sensitivity. In addition, many have speculated that cross-talk may occur between the receptors involved in the angiotensin II and the insulin signaling pathways; however, this remains unproven. Dr. McMurray noted that clinicians may prefer to think of a RAS blocker, such as valsartan, as opposed to other blood pressure lowering medications in hypertensive patients with impaired glucose tolerance or at high-risk for developing diabetes; however, according to the results of this trial, the increase in incident diabetes was not associated with any change in cardiovascular outcomes.

— by Sanjay Trehan

8. Conference Preview #1: American Diabetes Association 70th Scientific Sessions

June 25-29, 2010 • Orlando, FL •
http://professional.diabetes.org/Congress_Display.aspx?TYP=9&CID=71390

Welcome to the main event! This year marks the 70th annual American Diabetes Association (ADA) Scientific Sessions, and it's clear that the conference organizers have pulled out all the stops to commemorate the occasion. Over 15,000 physicians, diabetes educators, industry professionals, and researchers (and their families!) are expected in Orlando this year. Given the later dates of the conference, the detailed schedule of over 300 oral and 1,500 poster presentations is not yet available – but the titles of the ~100 published symposia, current issue sessions, and lectures certainly speak for themselves. The big trials reporting during the symposia will include STAR3 (insulin pump/CGM vs. SMBG/MDI) and HEALTHY (comprehensive middle-school based intervention to reduce risk factors for type 2 diabetes in youth), and we hope for updates from the BARI-2D, ACCORD, and ADVANCE trials as well. Also new this year are guided audio tours highlighting new developments from the poster hall (this could be seriously great) and the President's Poster Session, hosted on Sunday evening. And, of course, we so hope you are planning to attend the Close Concerns/TCOYD Diabetes Forum on Monday night. Below are a few chronologically ordered highlights we selected from the preliminary program – we look forward to seeing you in Orlando! Closer Look readers note that we'll be sending you a more detailed preview when we know more about oral sessions – if you have questions about this, please contact alisa.bekins@closeconcerns.com.

Highlights

Friday (June 25)

- **(2:00 - 4:00 pm) Clinical Role of TZDs in 2010.** While the effects of rosiglitazone (GSK's Avandia) on cardiovascular outcomes again captured the headlines this year, we will be looking forward to hearing more on the use of TZDs as preventative therapy, a cause strongly championed by Ralph DeFronzo, MD (University of Texas Health Science Center, San Antonio, TX) in the past

years. The always compelling Dr. Philip Home, DM, DPhil (Newcastle University, Newcastle, UK) will lead the session entitled "Has the Dust Settled? What is the Effect of TZDs on Cardiovascular Disease Risk After All?" so we will be expecting updates and informal cuts from the RECORD trial data as well – an apt prelude to the FDA Advisory Committee meeting on Avandia in mid-July.

- **(4:15 - 6:15 pm) Tailoring Diabetes Treatment Priorities in the New Age of Cardiometabolic Risk Management.** As healthcare professionals shift away from the glucocentric approach to diabetes care, the management of cardiovascular risk factors is receiving increasing focus – especially in terms of the cardiometabolic effects of various treatments. In particular, we look forward to discussions on the implications of personalized cardiovascular risk management goals for treatment guidelines from Patrick O'Connor, MD (HealthPartners Research Foundation, Minneapolis, MN) and the cost-effectiveness of various treatments toward the minimization of cardiovascular risk from Brian Denton, PhD (North Carolina State University, Raleigh, NC).
- **(4:15 - 6:15 pm) The Implications of U.S. Health Care Reform on the Care and Prevention of Diabetes.** The newly passed insurance reform was viewed as a strong step forward for patients with diabetes wrestling with the cost of care, particularly due to changes in the way insurance providers are allowed to address pre-existing conditions. However, we hope to gain a more comprehensive understanding of the impact of reform on all levels of diabetes care, including patients, providers, preventative services, and the payment system.

Saturday (June 26)

- **(8:00 - 10:00 am) Combination Therapies for Type 2 Diabetes From the Get-Go – Are We There Yet?** Given the impact of progressive beta cell loss on treatment failure, numerous agents have been volunteered and approved for use in early combination therapy. This session will cover the potential use of these agents in early therapy, with presentations from a star-studded panel including Bernard Zinman, MD (University of Toronto, Toronto, Canada), Robert Cuddihy, MD (International Diabetes Center, Minneapolis, MN), and Hannele Yki-Jarvinen, MD (University of Helsinki, Helsinki, Finland).
- **(8:00 - 10:00 am) Joint ADA/The Lancet Symposium.** The Joint ADA/Lancet Symposium has provided a comprehensive snapshot of the latest developments in diabetes since it was founded a couple of years ago – this year's session will include a recap of clinical trial data from an array of therapies, including dapagliflozin (BMS/AZ), Technosphere insulin (MannKind's Afrezza), and exenatide once-weekly (Amylin/Eli Lilly/Alkermes' Bydureon). While it's unclear if any new data will be presented during the session, we look forward to hearing the perspectives of the phenomenal slew of speakers, which include ADA President Richard Bergenstal, MD (International Diabetes Center, Minneapolis, MN) and former recipient of the ADA Outstanding Physician Clinician in Diabetes Award Daniel Lorber, MD (Weill Medical College of Cornell University, New York City, NY).
- **(1:45 - 3:45 pm) Joint ADA/EASD Symposium: Glucagon-Like Peptide-1 – From Secretion to Function.** While the majority of this symposia will be devoted to better understanding the physiological mechanisms of GLP-1 action, we'll be looking forward to the discussion on combination GLP-1/glucagon receptor hybrid therapy, presented by Matthias Tschoep, MD (University of Cincinnati, Cincinnati, OH). With numerous companies investigating combination GLP-1 therapy (sanofi-aventis, Novo Nordisk on GLP-1/insulin; Marcadia on GLP-1/GIP dual agonist; Transition Therapeutics on GLP-1/glucagon receptor dual agonists) this will likely continue to be a hot topic going forward.

- **(1:45 - 3:45 pm) Glycemic Outcomes and Acute Complications: MDI or the Pump – Which Is Best?** This "Current Issues" session will certainly be well attended, as ADA President Dr. Bergenstal will debate Thomas Blevins, MD (Texas Diabetes and Endocrinology, Austin, TX) over the benefits of MDI vs. pump therapy. Given that conclusive evidence in support of either therapy remains elusive, we will be interested to see how each speaker frames his argument.
- **(4:00 - 6:00 pm) Should New Diabetes Drugs Submitted to the FDA Have a Higher Bar for Cardiovascular Safety Than Other Drugs?** This session needs no introduction. Since it was issued in 2008, the FDA's cardiovascular guidance to industry has been challenged for potentially delaying the approval of new diabetes drugs – we heard this sentiment echoed at last year's ADA. In this session, original proponent Steven Nissen, MD (Cleveland Clinic, Cleveland, OH) will defend the increased cardiovascular safety standards against former FDA Director of the Division of Metabolism and Endocrinology Products David Orloff, MD (Medpace, Cincinnati, OH) – gleaning from our interview with Dr. Orloff in *Diabetes Close Up* #99, we expect a very thorough, evidence-based debate.

Sunday (June 27)

- **(8:00 - 10:00 am) Controversies Relating Cancer with Diabetes, Obesity, and Insulin.** The link between insulin and cancer has been a hot topic at many meetings this year. With presentations from heavy hitters Jeffrey Johnson, PhD (University of Alberta, Edmonton, Canada), Derek LeRoith, MD, PhD (Mt. Sinai School of Medicine, New York City, NY), John Lachin, ScD (George Washington University, Washington, DC), and Jay Skyler, MD (University of Miami Diabetes Research Institute, Miami, FL), we hope this session will be the last word on the lessons learned from the four *Diabetologia* articles – and more importantly, what still needs to be understood about the link between diabetes, antidiabetic therapies, and cancer.
- **(10:15 am - 12:15 pm) President, Medicine & Science Address and Banting Lecture.** This year's prestigious Banting Lecture will be given by former ADA President Robert Rizza, MD (Mayo Clinic, Rochester, MN), who will discuss "The Liver as a Prime Target for Individualized Therapy in Diabetes" – Dr. Rizza has long been renowned for his understanding of the mechanisms underlying type 2 diabetes and attention to detail, so we expect a very thorough discussion of rational approaches to personalized therapy. Current ADA President Dr. Bergenstal will also deliver an address titled "Patient-Centered Team Diabetes Care in an Era of Health Care Reform – Lessons from Three Leaders in the Field." Dr. Bergenstal voiced strong support for team-based care in our interview with him in *Diabetes Close Up* #100, and we look forward to hearing more on how he hopes to prioritize this approach within the ADA.
- **(2:00 - 4:00 pm) Joint ADA/JDRF Symposium: The Artificial Pancreas – A Goal within Reach?** In our interview with former JDRF President and CEO Dr. Alan Lewis (see *Diabetes Close Up* #96), Dr. Lewis anticipated success with the Artificial Pancreas Project (APP) within five years. We look forward to hearing an update on the development in this session, led by highly respected scientists and clinicians Aaron Kowalski, PhD (Juvenile Diabetes Research Foundation, New York, NY), William Tamborlane, MD (Yale School of Medicine, New Haven, CT), Marilyn Ritholz, PhD (Joslin Diabetes Center, Boston, MA), and Roman Hovorka, PhD (University of Cambridge, Cambridge, UK).
- **(4:15 - 6:15 pm) Newer Insulins – As They Approach Availability What Should We Know about Them?** Numerous companies are involved in the development of the next generation of insulins, and many are just on the horizon. We expect key insights during this session on the value and potential of the ultra-rapid acting insulins (e.g., Biodel's VIAject, Halozyme's PH-20 combined insulins) from Michael Weiss, MD, PhD (Case Western Reserve

University, Cleveland, OH), the next generation of long-acting basal insulins (e.g., Novo Nordisk's insulin degludec, sanofi-aventis' SAR161271) from Satish Garg, MD (University of Colorado School of Medicine, Denver, CO), and alternative insulin delivery methods (e.g., MannKind's Afrezza, Generex's Oral-Lyn) from William Cefalu, MD (Louisiana State University, Baton Rouge, LA).

- **(4:15 - 6:15 pm) Tactics and Controversies in the Management of Hyperglycemia in the Hospital.** As the title of this symposium alludes to, in-hospital glycemic control continues to be controversial, particularly in the light of the underwhelming NICE-SUGAR study. Mary Korytkowski, MD (University of Pittsburgh, Pittsburgh, PA) has delivered numerous talks this year on how the outcomes trials should guide glycemic targets – we look forward to her presence during this symposium, in addition to that of Mikhail Kosiborod, MD (St. Luke's Hospital, Chesterfield, MO), Mercedes Falciglia, MD (University of Cincinnati, Cincinnati, OH), and Stephen Clement, MD (Georgetown University, Washington, DC).
- **(4:15 - 6:15 pm) HEALTHY Study – Middle School-Based Intervention to Reduce Diabetes Risk.** The HEALTHY study is examining the effects of one of the most comprehensive lifestyle interventions for youth we've seen to date, comprised of changes in food service, physical activity, family involvement, and social environment, as well as health-based curriculum and projects. If the intervention proves effective, we'll also look for some indication of how such a program could be implemented on a broader basis.
- **(4:15 - 6:15 pm) Alternative Cellular Sources for Beta Cell Replacement Therapy – Today and Tomorrow.** Though there are certainly a number of hurdles to overcome with beta cell replacement therapy, researchers have been pursuing a range of different approaches – we expect a thorough review of the latest developments in islet transplantation, led by Camillo Ricordi, MD (Diabetes Research Institute, Miami, FL), Hsun Teresa Ku, PhD (Beckman Research Institute, San Francisco, CA), Rene Maehr, PhD (Harvard University, Boston, MA), and Colin Weber, MD (Emory University, Atlanta, GA).

Monday (June 28)

- **(8:00 - 10:0 am) Nutrient-Gut-Brain Modulators.** Always extraordinary Lee Kaplan, MD, PhD (Harvard School of Medicine, Boston, MA) will lead this session on the complex physiology of obesity as well as present on the mechanisms of type 2 diabetes remission with bariatric surgery. The session promises to be enlightening with multi-faceted discussions on the influence of the central nervous system and endocrine function on obesity—the conversation seems to be broadening beyond the handful of incretin hormones previously binding the lexicon.
- **(2:15 - 4:15 pm) Updates on GLP-1 Agonists.** GLP-1s have slowly been edging their way into the spotlight this past year, and we expect the class to be center-stage in the upcoming year with Novo Nordisk's Victoza (liraglutide) hitting its stride and long acting GLP-1s on the horizon (most immediately, Amylin/Lilly/Alkermes' Bydureon). Steve Edelman, MD (University of California at San Diego, San Diego, CA) will chair the session, and we look forward to hearing a presentation on the cardiovascular benefits of GLP-1s, an update on long-acting GLP-1s on the horizon, a safety-minded discussion on GLP-1s and pancreatitis, and a more novel topic for us: GLP-1s and transplants.
- **(4:30 - 6:30 pm) Will DPP-4 Inhibitors Replace Sulfonylureas?** A very current issue indeed will be discussed by Julio Rosenstock, MD (University of Texas Southwestern Medical School, Dallas, TX). It's hard to attend any major meeting without hearing a few derisive comments concerning sulfonylureas, but the fact remains that they are still very widely prescribed (and inexpensive). The pharmacological landscape has changed quite a bit since the reigning

generic sulfonylureas hit the market and there are now agents with attractive side-effect profiles and potentially other benefits (i.e., beta-cell preservation) that may justify the increased cost of choosing alternative therapies early in the spectrum of diabetes management.

- **(5:00 – 7:00 pm) Close Concerns/TCOYD Fourth Annual Diabetes Forum.** For more details and the way to sign up, please see our letter from the editor in this issue.

Tuesday (June 29)

- **(8:00 - 10:00 am) The Potential of SGLT-2 Inhibitors for Diabetes Management.** The excitement and interest in the emerging SGLT2 inhibitor class has been growing more and more palpable over the previous year—at the 69th Scientific Sessions, presenters had to focus on convincing the audience that using the kidney (and urinary glucose excretion) as a tool in this disease wasn't a crazy idea. This year, with several companies working on distinct compounds in the class and more clinical and safety data available, we expect more depth to be added to the discussion by this session led by Bernard Zinman, MD (University of Toronto, Ontario, Canada).
- **(8:00 - 10:00 am) Late Breaking Clinical Studies.** As always, we are highly anticipating the session on Late Breaking Clinical Studies, to be led this year by Richard Bergenstal, MD (International Diabetes Center, Park Nicollet, MN). In particular, we look forward to results from the STAR 3 trial, a one-year randomized controlled trial comparing sensor-augmented pump therapy to multiple daily injection therapy. While it's clear CGM is already here to stay, there is still considerable debate about the clinical impact of the sensor and a clear demand for more outcomes data. We will also hear more on BARI2D (looking at outcomes for patents using rosiglitazone, in particular) and ADVANCE (focusing on severe hypoglycemia and risk of vascular events/death).
- **(10:15 am - 12:15 pm) Results of the ACCORD Clinical Trial.** The everlasting gorilla in the china shop, the ACCORD trial will be further discussed in a session led by Denise Simons-Morton, MD, PhD (Division of Cardiovascular Sciences: National Heart, Lung, and Blood Institute, Bethesda, MD). We are not sure how much of this will be "new" per se, but we expect the presentations to offer more nuance beyond the major outcomes still ringing in our ears. In any event, the debates generated by the trial rage on and we are excited to hear any new insights.

— by Eric Chang and Jessica Swienckowski

9. Conference Preview #2: Children with Diabetes – Friends for Life Conference 2010

June 30 – July 4 • Orlando, Florida • http://www.childrenwithdiabetes.com/activities/orlando2010/

Every year, we look forward to the Children with Diabete s(CWD), Friends for Life conference for the collective 'we-can-conquer-the-world' spirit and its A-list faculty (Dr. Ed Damiano, Dr. Stu Weinzimer, Gary Scheiner, Dr. Richard Rubin, and Dr. Henry Anhalt, just to name a few). The excitement at CWD is both inside and outside of the formal lecture sessions, and especially in the bustling exhibit floor. As expected, the meeting will have a heavy focus on diabetes devices (continuous glucose monitoring, insulin pumps, and closed loop systems) as well as the everyday challenge of diabetes management. We always cherish our time at FFL and look forward to reporting from this wonderful meeting.

Thursday (July 1)

- **The Artificial Pancreas Project.** Closed Loop experts Stuart Weinzimer, MD (Yale School of Medicine, New Haven, CT) and Edward Damiano, PhD (Boston University, Boston, MA) will lead a session on the Artificial Pancreas project. We look forward to a comprehensive update on the Artificial Pancreas as well as more details on the studies they plan to conduct.
- **Getting it Right: Accuracy in Glucose Measurement.** Chair of the Interagency Artificial Pancreas Working Group, Arleen Pinkos, MT (ASCP) will lead a discussion on the accuracy of blood glucose meters. Given the recent regulatory controversy over the accuracy of glucose meters, we are very interested to hear her perspective.
- **Diabetes Research Institute (DRI) Research Update.** There will be two separate DRI Research Updates on Thursday, July 1. Norma Kenyon, PhD (DRI, Miami, FL) will speak on the potential for a biological cure for diabetes and Cherie Stabler, PhD (DRI, Miami, FL) will provide an update on tissue engineering for the treatment of diabetes.
- **Infusion Sets and Sensors.** Natalie Bellini, RN, CDE (Senior Territory Manager at Animas Corporation) will provide a detailed talk on how to choose, use, and maintain infusion sets and sensors.

Friday (July 2)

- **Prevention and Treatment at Onset.** ADA Public Policy Leadership Award Recipient Desmond Schatz, MD (University of Florida College of Medicine, Gainesville, FL) will discuss the current therapies in development for the prevention of diabetes and for treatment at the onset of diabetes.
- **Managing Hypoglycemia.** CDE extraordinaire and diaTribe (diaTribe.us) advisory panel member Gary Scheiner (Integrated Diabetes Services, Wynnewood, PA) will discuss how to properly manage hypoglycemia. He is also leading two sessions on Thursday, "Pumping Basics" and "Making Sense of Sensor Data."

— by Sanjay Trehan

10. Diabetes Comings and Goings

- **Michael Berelowitz, MD** joined OraMed's Board of Directors on May 18, 2010. Dr. Berelowitz is currently the Senior Vice President and Head of Clinical Development and Medical Affairs in the Specialty Care Business Unit at Pfizer, where he has been for 15 years.
- **John Brooks III** has been appointed as the Chairman of Joslin Diabetes Center's Board of Trustees on May 17. Brooks, whose son was diagnosed with diabetes at the age of three, is replacing Kevin Conley. He is currently a principal at Healthcare Capital Consulting and has founded three life sciences companies, including Insulet.
- **Alan Lewis, MD** resigned as the President and CEO of JDRF for "personal reasons" on May 13, 2010. While Dr. Lewis will be available to JDRF in the transition period, JDRF Board member Frank Ingrassia will become acting CEO. In the meantime, the Board committee will be conducting a search for a new president.
- **Linda Higgins, PhD** was appointed as the President and CEO of InteKrin Therapeutics on May 10, 2010. Dr. Higgins most recently served as the company's Chief Scientific Officer and Chief Operating Officer.

- **Denny Lanfear** was selected as the Chairman of InteKrin Therapeutics' Board of Directors on May 10, 2010. Lanfear founded the company and recently stepped down from the President and CEO positions at InteKrin. InteKrin is routinely cited for its top-notch management team; we have been very impressed by Lanfear's leadership and the incredible bench strength at the company. There is great confidence in Higgins taking the reins, even as there is disappointment that Lanfear will be less visible in his Chairman role than he was as CEO.
- **Michael Miller** was appointed as the Chief Commercial Officer at Vivus on May 3, 2010. Miller will report directly to CEO Leland Wilson and will lead the commercial strategy for Qnexa, if approved.
- **Robert O'Holla** was named the Executive Vice President of Regulatory Affairs at CeQur, effective May 1, 2010. O'Holla was previously at J&J for 33 years and served as the company's Worldwide Vice President of Regulatory Affairs.
- **Roman Skowronski, MD, PhD** was selected as that Vice President of Clinical Development at InteKrin Therapeutics on April 23, 2010. Most recently, Dr. Skowronski was the Vice President of Clinical Development at AcelRx Pharmaceuticals.
- **Wendy Dixon, PhD** was appointed to Orexigen's Board of Directors on April 21, 2010. Dr. Dixon is currently the President of Global Marketing and Chief Marketing Officer at Bristol-Myers Squibb.

11. DCU Stock Chart and Final Thoughts

	28-May-10	30-Apr-10		30-Nov-09		28-May-09		IPO		Market Cap
ALKS (Alkermes)	11.36	13.11	-13%	8.98	26%	8.25	38%	5	127%	1.1B
AMLN (Amylin)	16.52	20.64	-20%	14.26	16%	11.24	47%	14	18%	2.4B
ARNA (Arena)	3.08	3.25	-5%	3.63	-15%	3.70	-17%	18	-83%	311.5M
BIOD (Biodel)	4.92	4.50	9%	3.78	30%	4.44	11%	15	-67%	117.5M
DXCM (DexCom)	10.53	10.95	-4%	10.95	-4%	5.05	-	5.33	98%	604.8M
ETRM (EnteroMedics)	0.36	0.54	-33%	0.51	-29%	2.30	-84%	12	-97%	16.1M
GSK (GlaxoSmithKline)	33.46	37.29	-10%	41.47	-19%	33.50	0%	8	318%	86.9B
HALO (Halozyme)	7.33	8.52	-14%	5.46	34%	6.69	10%	-	-	672.3M
HGSI (Human Genome Sciences)	24.76	27.69	-11%	27.82	-11%	2.14	1057%	7.68	222%	4.6B
ISIS (ISIS Pharmaceuticals)	9.20	10.76	-14%	10.71	-14%	13.63	-33%	21.5	-57%	911.6M
MNKD (Mannkind)	5.56	6.95	-20%	7.26	-23%	6.62	-16%	2.31	141%	630.8M
NVO (Novo Nordisk)	76.82	82.10	-6%	66.72	15%	51.24	50%	14	449%	53.2B
OREX (Orexigen)	5.44	6.78	-20%	6.67	-18%	3.37	61%	29.2	-81%	256.9M
OSIP (OSI Pharmaceuticals)	57.38	58.67	-2%	33.31	72%	34.04	69%	12	378%	3.5B
PODD (Insulet)	14.57	13.81	6%	12.26	19%	7.06	106%	170	-91%	552.9M
TTHI (Transition Therapeutics)	4.40	3.90	13%	8.00	-45%	3.88	13%	15	-71%	102.2M
VVUS (Vivus)	12.66	10.19	24%	8.12	56%	4.97	155%	1.25	913%	1B
XOMA (XOMA Limited)	0.44	0.66	-33%	0.75	-41%	0.78	-43%	14.25	-97%	115.2M
S&P 500	1089.41	1186.68	-8%	1095.63	-1%	906.83	20%	-	-	-
NASDAQ	2257.04	2461.19	-8%	2144.60	5%	1751.79	29%	-	-	-

Overall, stocks in the diabetes and obesity index declined with the S&P 500 and NASDAQ since DCU #100. In general, the equity markets were extremely volatile in May after the Dow Jones Industrial Average (DJIA) shot down an unprecedented (and still unexplained) 1,000 points before bouncing back on May 6. Vivus weathered the storm particularly well, gaining 24% over the last month alone. At the end of April and throughout May, the company presented the results of studies demonstrating beneficial effects of Qnexa on weight-related comorbidities. Transition Therapeutics also increased 13% in the last month; while little "news" was announced during the company's recent F3Q10 financial update, it reported progress on the GLP-1/gastrin and GLP-1/glucagon receptor agonist therapies. Investors were also bearish on Xoma after it reported 1Q10 results – despite the 33% drop, we are eager to see more

detailed results on the company's lead diabetes candidate, XOMA 052, at this year's ADA meeting. As usual, we look forward to clinical results, partnerships, and regulatory decisions to drive the index in the coming months.