DIABETES CLOSE UP

Diabetes Close Up
August 2007, No. 71
The Quiet Heroes

The Shorter Version

From the Editor:

In the diabetes world, the physicians and the researchers are the rock stars – they get the headlines, make the breakthroughs, snare the credit. We certainly respect them as much as anyone, but we also believe the educators are the quiet heroes in diabetes care. They don't get the attention and certainly not the money their counterparts do, but they often spend the most valuable time with patients – listening, teaching, encouraging, and consoling. Our admiration for educators is why we value so highly the annual meeting of the American Association of Diabetes Educators, which we cover in this issue. The best way to reach the patients, with the latest technology or therapeutic insights or research findings, is to reach the educators. Give them the ball, and they won't drop it.

So, it was a quieter week this week, until Novo Nordisk announced lira data and Medtronic announced new deals with J&J and Bayer – all in the space of about 24 hours. Exciting times - we give our take on all inside, including the pump market, which is continuing to show remarkable growth. And, that reminds me! On a related note – we published a new issue of diaTribe today, our sister publication for patients with diabetes – see diaTribe #5 at www.diatribe.us and don't miss Jim Hirsch's delve into disposable pumping and continuous monitoring ("CGM has the opportunity to transform care") at http://www.diatribe.us/issues/5/test-drive.php.

This issue, we have an interview with the inspiring, inspired Jeff Hitchcock, who founded "Children with Diabetes" several years after his daughter, Marissa, was diagnosed. We love Jeff because he shows how one person can make a difference. Along with his colleague Laura Billetdeaux, and a host of dedicated volunteers, he runs a Web site and sponsors conferences that have benefited countless families affected by diabetes. We believe you'll enjoy his comments on, among other things, what industry does well and what it needs to do better.

And finally, we hope everyone enjoys their final days of summer….we know we will.

--Kelly L. Close

MAJOR HEADLINES, DCU #71

In this issue:

Blogwatch - See below for blogs since our last monthly newsletter. You can see any update online at http://www.closeconcerns.com/ as well as subscribe to the RSS blog feed. We've not been too active on our own blog but now that Kelly is back from maternity leave, it'll get more active. Stay tuned!

- August 1: Presidential candidate Mike Huckabee, at AADE
- July 28: Obesity abounds; new maps out

Besides writing our own blog, we also write a blog for Revolution Health called "Up Close and Personal" on life with diabetes. You can find it at www.revolutionhealth.com/blogs/kellyclose.

- August 20: Obesity and diabetes puzzle
- August 15: Healthcare in America: Not what it should be
- July 28: Compelling diabetes YouTube video / Check out obesity maps
- July 26: The Exubera commercial
- July 17: My favorite diabetes meeting of the year, bar none ...~
- July 11: Back from ADA

Our favorite YouTube videos in diabetes this month

- "Hope is a Cure" http://www.youtube.com/watch?v=Z2uE0TlBZGc
- "Why diaTribe?": http://www.youtube.com/watch?v=oDz2k8SnK6w
- "Pre Diabetes": http://www.youtube.com/watch?v=hEckq0aIOJg

Coming soon in DCU…

- Our review of the 43rd European Association for the Study of Diabetes (EASD) Annual Meeting, held September 18-21 in Amsterdam. We're also headed to Boston to report on the Cardiometabolic Health Congress (CHC), held at the end of September. Stay tuned…

The Longer Version

1. Quotable Quotes in Diabetes:

AADE Opening Ceremony – "Changing Your Life to Have a Life" with Mike Huckabee (Former governor of Arkansas and 2008 presidential candidate)

- Mr. Huckabee's two rules of thumb for nutrition: 1) *"Whatever was not a food a hundred years ago is not a food now"* and 2) *"If it comes through the car window, it isn't food."*
- On the dire state of diabetes in America: "*If we don't do something soon [about diabetes]… I'm not sure we'll be able to fully recover."*
- Regarding America's health care crisis: *"We don't have a health care system; we have a sick care system."*

From AADE symposia:

- Pharmacist Susan Cornell commenting on the rapid progress in diabetes treatment options: *"Diabetes changes faster than I change clothes."*
- Educator Joe Solowiejczyk discussing family involvement in pediatric management: *"If you think your kids are going to come back from diabetes camp saying, 'Mom, Dad, I understand the seriousness of this disease, I'm sorry for all of the pain I've caused you and Timmy, and I'm going to manage it better,' then smoke another bowl."*
- Eric Finkelstein, PhD, on the economics of obesity: "*The opportunity cost of preparing foods from scratch continues to increase relative to purchasing prepared and pre-packaged foods."*
- Dr. Bruce Bode noting that DexCom has been able to get two CGM devices on the market while Abbott is still struggling to get the Navigator through the FDA: *"DexCom has an amazing ability to get through the FDA approval system."*
- Linda Valentino, RN, on transitioning patients from inpatient to outpatient care: *"There are three core knowledge items that patients must know: what to eat, how to take their diabetes medication, and how to check their blood sugar."*
- Dr. Neil White on type 2 diabetes in children: *"It's clear to me that lifestyle intervention is the first line of treatment, but it's also clear to me that lifestyle is unlikely to be implemented successfully in the long term… The consensus in children is that type 2 subjects who are stable should go on metformin first – it's the only OAD approved in children… There's no consensus about what to do once metformin fails."*
- Dr. Om Ganda on insulin delay: *"Don't delay insulin when two conventional oral drugs fail… When patients fail on two oral medications, we can add a third oral agent, or an incretin mimetic… However, insulin is the best choice if a patient's A1c is over 8%, because most patients with A1c over 8% will not achieve goal on another OAD."*
- CDE Ginger Kanzer-Lewis, during the Pfizer product theatre: *"Insulin is insulin, Exubera is insulin. The fact that we don't inject it doesn't mean it's not as valuable"*

From our DCU interview with Jeff Hitchcock, founder of Children With Diabetes (CWD):

- *"I think there's this enormous misperception about type 1 versus type 2 in the general population, and a lack of appreciation for the dramatic advances that medicine has made in caring for type 1 diabetes in the last 10 or 20 years."*

- *"When I look back on almost 18 years of living as a parent of a child with diabetes, and I look at the institutions or organizations that have made the biggest impact on my daughter's life, it has been industry. When we compare glucose monitors from 1989 to today, we go from the best meter on the market that took 120 seconds and a drop of blood that would have made a bricklayer cry, to meters today that are in the three- to five-second range, with sub-microliter volumes… and integrated data management or connections to computers to help identify patterns and improve management strategies."*
- *"Having diabetes is not trivial. It requires a lot of attention. It means that you do things that other people don't. But the alternative is, you're not there. And to me that is a simple decision."*
- *"I can't retire until we have scheduled the Children Who Used to Have Diabetes Conference."*

2. diaTribe FingerSticks

—by Daniel A. Belkin

3. DCU Company Watch

- **Medtronic -Medtronic Diabetes is posting record results: its $241 million in revenue (another quarterly record) is up 23% versus a year ago.** Medtronic announced two exciting deals with industry titans J&J LifeScan and Bayer Diabetes the same day its robust results were announced, both of which should bolster Medtronic Diabetes' weakest link – the absence of a partner with a robust, reliable blood-glucose monitor to provide wireless data transmission capability between monitors and Paradigm pumps.

The new meters have been promised for the first half of 2008. While Medtronic's deal with J&J/LifeScan may not seem perfectly intuitive since J&J owns Animas, a competing insulin pump, to us it makes perfect sense. First, J&J wants access to Medtronic's high-frequency pump users (we believe pumpers test ~6-8x/daily in the US, whereas even the average LifeScan meter owner likely doesn't test more than ~3x/day); and second, importantly, this keeps LifeScan's blood glucose monitoring competitors from gaining direct access to this valuable group. By our estimate, US Medtronic pumpers generate blood glucose monitoring revenue that is a multiple of Animas total revenues – and higher margin revenues at that, likely around $250-$300 million total. In sum, while a few say this deal is counterintuitive because J&J owns Animas "so-how-could-they-be-supplying-a-competitor-with-strips" we certainly understand that they would rather supply Medtronic than have a competitor do it! Overall, we guess that J&J picks up an incremental $125-$250 million in blood glucose monitoring revenue (we're assuming they already have perhaps 50% of these customers) – that can fund some real LifeScan and Animas R&D! There are fewer pumpers abroad, but we still believe Bayer will see upwards of $75 million in incremental revenue based on this deal – and will gain a valuable installed base of type 1s to boot, a major strategic advantage for its business.

We estimate that insulin pumpers globally generate $300-$400 million in blood glucose monitoring revenue annually (our math assumes ~350,000 pumpers, $0.40-$0.50/strip depending on geography, 4-7 tests/day). We view this as excellent news for Medtronic's pumpers as well as Medtronic's partners -- J&J/LifeScan, partnering with US Medtronic Diabetes, gets access to ~250,000 pumpers -- Bayer gains access to 100,000-plus pumpers internationally with an ex-US deal. Longer-term, Medtronic may push all its pumpers toward its continuous monitoring system and away from frequent blood glucose monitoring – but that is unlikely to happen anytime soon – and meters are always needed to calibrate! At the end of April, Medtronic estimated 15,000 people in the US on continuous monitoring. CGM sales "beat plan" this quarter, though the plan itself wasn't disclosed – key questions include what percent of new purchasers convert to consistent users, whether the starts are successful, whether they keep using the technology, and how much total time they are on the technology.

Medtronic hasn't disclosed the distribution details beyond noting that a meter would be included with each pump sold (no word on strips). Historically it also made strips available by mail order along with pump disposables. If Medtronic does this again, there might be nice revenue benefit for Medtronic, but even more importantly, it will also make customer service more efficient as it likely won't need to respond to as many problems. Bottom line, we see the deal as positive for the entire pump industry because Medtronic and partners will do more diabetes management education, undoubtedly pushing pump therapy.

- **Novo Nordisk—LEAD results out, on the path to GLP-1 submission**. The results for LEAD 1 and LEAD 2, Novo Nordisk's phase 3 trial for its GLP-1 compound liraglutide, were released on August 20, providing a fast follow up to LEAD 5 results, which were released just prior to ADA.. As a reminder, LEAD 5 compared liraglutide and Lantus, and showed statistically significant reductions in A1c (0.2) and weight. LEAD 1 and LEAD 2 were mixed in terms of significance of A1c reduction but positive in terms of weight loss and overall side effects, needle size, etc.

  LEAD 1 was a 6-month trial (n=1,026) testing liraglutide versus rosiglitizone (Avandia). It was conducted globally but not in the US or Japan. The trial was designed to show the effect of treatment with liraglutide when added to existing glimepiride (a sulfonylurea or SFU) therapy and to compare this to both SFU monotherapy and to rosiglitazone as add-on therapy to SFU. Liraglutide patients got to statistically significant better glucose control than Avandia, and "around 40%" of those on liraglutide reached the ADA A1c target of less than

7%. Weight loss was 2 to 4 kg lower in the liraglutide group than the rosiglitazone group. It is difficult to interpret the data because the release did not disclose the baseline A1c, weight, and nausea rates in each study; comparisons to other GLP-1 compounds will ultimately best be done head-to-head. In LEAD 1 and LEAD 2, we aren't sure what the patient profiles were at the beginning of the study, and what the primary efficacy analysis was – we will look forward to learning more about this when the data is published, likely in 2008. LEAD 2 was a 6-month trial (n=1,026) with multiple arms. This trial was designed to show the effect of treatment with liraglutide when adding to existing metformin therapy and to compare it with the effects of metformin monotherapy and combination therapy of metformin and glimepiride (SFU). In this trial, the A1c improvement in the Lira group compared to the SFU group was not statistically significant. Weight loss results in this trial were also 2 to 4 kg, and it will be very interesting to follow weight loss over time to see if it is as progressive as it has been for Amylin's Byetta, and to see if there are as many apparent "super-responders" – people in the top quartile losing upwards of 20-30 pounds or more, etc. While the lack of a statistically significant A1c reduction versus an SFU is not encouraging, we wonder whether there is an "ADOPT effect," i.e., where the SFUs performed the best of the drugs in the first six months but where the performance began to lag very quickly. Either way, we still believe that GLP-1s will steadily replace SFUs over time, even if people don't begin to take them as early on in disease therapy as SFUs are currently taken now. Overall, we certainly see arguments in favor of Liraglutide as associated with weight, convenience, and economics versus other orals. Novo's use of a 32-gauge needle is a slight advantage over Byetta's 31-gauge needle, though how patients perceive it versus a lower-gauge once-weekly needle remains to be seen – once weekly is clearly a major advantage, and it will be interesting to see how much "hassle factor" emerges with both therapies, if any. It will also be key to see how primary care marketing emerges with each therapy –that's the name of the game after the endo thought leaders weigh in (so to speak).

Impressively, over 2/3 of the people in phase 3 LEAD trials have now reported. Through LEAD, Novo Nordisk looks to be testing Lira in almost every segment of the type 2 population – this should be very useful for their publishing, reimbursement, and coverage strategy – they have very impressive formulary coverage on the insulin front and we assume this will be a strength as they move into marketing other large molecule diabetes drugs. We do believe there are a number of sub-segments of type 2s, as well as overweight people, for whom liraglutide could be effective and we think the subsegment analysis should prove very interesting. We eagerly await the results from LEAD 3, a year-long monotherapy trial, to be reported in early 2008, as well as LEAD 4, a US and Japan trial that is designed to show the effect of liraglutide when added to existing rosiglitazone and metformin combination therapy and to compare it with therapy with rosiglitazone and metformin alone - those results from LEAD 4 are due in late 2007.

- **Insulet 2Q07—Strong revenues, users up 40% sequentially to 2,450:** CEO and President Duane DeSisto discussed strong revenue growth in a short period for Insulet – revenues of $3.2 million rose from $2.0 million in the first quarter, the first the company reported publicly, and $0.9 million a year ago. The number of OmniPod users rose an impressive 40% from 1,750 to 2,450 since 1Q – we believe strong word of mouth for the product, Midwest sales force expansion, and high sales force productivity, boosted by a very successful sampling program (feeling is believing), drove the increase. Further sales force expansion to the South and West at the end of the quarter bodes well for the second half. About 75% of new users are still coming from MDI (multiple daily injections), underscoring continued market expansion potential. In managed care, the company noted it has contracts with plans that cover 96 million lives and said it was working on additional contracts with new insurers. This is an increase from 92 million covered lives in the first quarter; given that there are ~180

million covered lives by our math (300 million people in the US minus 35 million each for Medicare and Medicaid and 50 million uninsured), we think the potential here is very high. Good manufacturing news was that Insulet got the first order of sub-assemblies from Flextronics during the quarter, and the company expects to complete its agreement with this partner to cover all OmniPods with the goal for costs at $15 or less per pod by the end of 2008 – given average selling price is $35, moving to a gross margin of 50-60% certainly sounds good. Management said that the high end of $10-$12 million guidance for 2007 revenue was more likely, given strong sales this quarter and strong demand – we certainly see upside potential since we imagine the number of pumpers at year end should easily approach 4,000. We continue to believe cost reduction is the major key for Insulet as is continuing to remain close to its customers, which Insulet has done very well to date. More progress on managed care will also be paramount – we see that coming, but slogging through it seems a little trying at times.

- **Transition Therapeutics—Now also trading on the NASDAQ:** On August 16, Transition Therapeutics, Inc. announced that they would begin trading on the NASDAQ under the symbol "TTHI." The biopharmaceutical company will continue to trade on the Toronto Stock exchange under the symbol TTH. Transition Therapeutics is developing two regenerative therapies for the treatment of diabetes – E1-I.N.T. and GLP1-I.N.T. – in partnership with Novo Nordisk.
- **Sirtris 2Q07—Starts phase 2a in type 2 diabetes:** On August 13, CEO Christoph Westphal provided an encouraging update on ongoing clinical trials in the company's first quarter as a public entity. Sirtris, founded in 2004, is exclusively involved in developing therapeutics that target sirtuins, a class of enzymes that play a role in aging. Sirtuin activation has been shown to increase lifespan and lower the incidence of many diseases related to aging in mice. Sirtuins such as SIRT1 are activated by a number of small molecules as well as calorie restriction, and they may mediate many of the benefits associated with a restricted diet. One molecule that has been shown to activate SIRT1 is resveratrol, a natural product that is present in red wine, though only in sub-therapeutic amounts. Sirtris has developed a proprietary formulation of resveratrol called SRT501 that achieves therapeutic levels in the blood in animal models. The company has synthesized over 3,000 similar compounds, and some appear to have up to 1,000 fold greater potency than SRT501.

  In diet-induced obese (DIO) mice, activation of SIRT1 by SRT501 reduces weight gain, fasting blood glucose, and insulin levels. Mice given SRT501 also have greater exercise tolerance and endurance than control mice. These mice consume more oxygen but the same amount of food, suggesting that SRT501 acts by increasing metabolic rate and mitochondrial biogenesis. SRT501 has completed phase 1a trials in healthy volunteers, and current enrollment is underway for two 90-person phase 1b studies in type 2 patients. Separately, the company is also conducting a phase 1b trial in patients with mitochondrial encephalopathy lactic acidosis and stroke-like episodes (MELAS is a rare, progressive and fatal disorder caused by a mutation in the DNA of mitochondria), for which SRT501 may receive orphan drug status. Data from all three phase 1b trials are expected at the end of 2007 to early 2008. In what seems like a smart move given all the interest in combination therapy, the company announced on August 21 the initiation of a phase 2a clinical trial with SRT501 (5g) as an add-on therapy to metformin; SRT501 has additive or synergistic effects with metformin in the DIO mouse model. The trial is expected to enroll 130 patients, and the results are expected at the end of 2008.

  Management suggested that SRT501 has the potential to treat a wide range of aging-related diseases, although it underscored that the company will focus for now on type 2 diabetes and MELAS. A number of other SIRT1 activators are also advancing, and will go into the clinic

next year. All of this is very early stage, but has definitely caught the fancy of Wall Street. On August 16, Sirtris founder David A. Sinclair and Leonard P. Guarente published a review in the MIT Tech Review highlighting the role of sirtuins in aging titled "Developing Drugs to Treat Diseases of Aging." As of June 30, Sirtris had cash equivalents of $136 million, compared with $50 million in December 2006. The company reported second-quarter net losses of $6.6 million, compared to a loss of $3.8 million a year ago, a bit higher than some analyst expectations. The company hopes to conclude 2007 with $115 to 118 million in cash, suggesting a quarterly burn of $10 million. Clearly the company will go after partnership opportunities as data emerges, which will be fascinating to track as we'll be able to see just how much Big Pharma wants into diabetes and how much they're willing to pay.

- **Bayer 2Q07—Bayer Diabetes Care posts industry-leading growth:** On August 7, Bayer reported that its Diabetes Care Unit, achieved impressive 2Q07 sales of €244 million (~$335 million), up 15% from €213 million last year (up 20% on a currency-adjusted basis). During his prepared remarks, CEO Werner Wenning mentioned that Ascensia achieved 20% growth: second quarter Ascensia product sales were €241 million (~$331 million), up 16% from €208 million last year (21% on a currency-adjusted basis). Notably, Bayer is the fastest growing player in the BGM market in the second quarter – it pioneered no-coding, which from talking to educators at AADE, is certainly a feature they welcome. Time is money!

- **Novo Nordisk 2Q07—Impressive growth in analogs and across the board:** In its August 3 earnings call, Novo Nordisk reported that its diabetes care franchise achieved sales of DKK 14.9 billion or ~$2.73 billion USD, up a strong 16% in local currencies (11% as reported). Diabetes accounted for 73% of the company's sales and for a striking 78% of its growth. Novo Nordisk expects 11-14% growth in local currencies for 2007, or 7-10% growth as reported. The company raised its guidance for operating profit to ~10% for 2007 (~20% in local currencies). Along with the rest of diabetes care, the modern insulin (analog) portfolio is growing particularly impressively. We believe the opportunity there continues to be significant as more people go on insulin and as insulin users continues to convert to analogs. Modern insulins represented 45% of diabetes care sales for 2Q, but 87% of 2Q diabetes care growth - this is the most remarkable statistic to us in all the reporting in that it suggests a very high growth profitability driver that still has room to go as modern insulin penetration is still low compared to where we believe it could go. Lots of upside! Management noted that Novo Nordisk is planning for the 2009 launch of liraglutide and that the same ramp up of resources would also be able to support its pulmonary AERx insulin launch. Management said that the remaining LEAD trials (LEAD 1-4) would report in the remainder of this year into 1Q08, with the twelve-month monotherapy trial to report last because of its longer duration. The two phase 3 Japanese trials will also report next year. Many eyes are on these reports

- **Sanofi-Aventis 2Q07—Lantus sales up 26% globally:** Lantus was Sanofi's fastest-growing pharma product, up 26% (reported) to €503 million ($668 million using the actual average exchange rate for the first half of 2007 of $1.33 per Euro). Lantus is now the leading commercial insulin product sold. 2Q sales rose 17% in Europe, 29% in the US, and 53% in other countries. As high as these growth rates seem, they actually represent a slowing of sorts; growth rates for the last quarter of 2006, for example, were 20% in Europe and 43% in the US. We didn't hear a lot about Apidra in terms of this conference call but we have been hearing strong sentiments from clinicians who prescribe it in pumps and have seen particularly good results. With respect to the FDA and rimonabant, management's discussion was very matter-of-fact about CRESCENDO (Comprehensive Rimonabant Evaluation Study of Cardiovascular ENDpoints and Outcomes), which will be the key trial to show longer-term impact of rimonabant use – results from this 17,000 person trial should emerge in 2010. CHMP (Eu's Committee for Medicinal Products for Human Use) did expand its warning

label for Acomplia (rimonabant) to include depression as an exclusion criterion, following re-evaluation post the FDA meeting. We will be eager to speak to healthcare professionals at EASD in mid-September about this.

- **Agamatrix—Jazz impresses at AADE with Bluetooth and on-screen glycemic variability**: We were really excited at AADE to see the new Jazz meter! That we now have a way to much better understand glycemic variability through blood glucose monitoring strikes us as a real step forward. Jazz is the first meter that we know of to offer a measure of glycemic variation (standard deviation) on the screen itself. Although conceptually, glycemic variation is far from a standard concept today, it's a terrific start to be able to put this valuable data into the hands of patients that choose it and to explain why it matters so they can reduce the highs and lows that they experience every day. To boot, glycemic variation is shown on the Jazz meter in an easy-to-understand way that will enable many patients to engage in their care and to more easily intensify and improve their diabetes self- management - themselves! This will really help patients who are eager to dig into data more easily develop an understanding of their meaning and improve their self-management. The meter's Bluetooth feature is an equally important addition – just have the meter within ten meters of your computer and in the data goes in – with very cool software, to boot, called ZeroClick. These are dramatic steps forward for intensively managed patients and for patients trying to do better; after all, patients can't improve self management unless they are given tools that are easy to use. Jazz has been submitted to FDA and we would expect to see it approved soon. And at AADE, if Jazz didn't catch people's attention, Agamatrix's generous giveaways certainly did – the first 1,000 people who wore a free WaveSense t-shirt at the exhibit were awarded an iPod shuffle.

- **DexCom 2Q07—SEVEN garners great reviews, quarterly revenue disappoints:** On July 31, DexCom reported revenues of $0.86 million, below expectations of $1.1 to 1.2 million. Net loss was $11.3 million, slightly above $11.2 million a year ago, and higher sequentially from $10.9 million in the first quarter. New CEO Terry Gregg led the call very ably and we believe there is great confidence in his ability. Poor revenue performance was blamed on a three-week delay from SEVEN's approval on May 31 to its availability toward the end of June. Customer growth decelerated – this would be expected when approval is close as patients wait to purchase next generation systems – and we will be interested to see what sort of rebound 3Q brings. A PMA supplement is with the FDA, for additional functionality on the SEVEN, allowing users to calibrate with any available meter.

  DexCom is in the final development stages of a third-generation short-term CGM product. The pivotal trial is expected to be completed early in 4Q, with filing shortly thereafter. The new device will have many improvements, including a 75% reduction in sensor size (DexCom already has the smallest sensor), needle gauge down from 26 to 28 (a major improvement), trend arrows, unique tones for high and low glucose alarms, vibrate-only capabilities, a snooze button, and a 12 and/or 24 hour screen. DexCom is pursuing EU markets for the SEVEN and has applied for a CE mark. Gregg said he has been asked by thought leaders to introduce the SEVEN in Europe, and will be discussing at EASD the potential for a 2008 introduction.

  On the business development front, management said partnering is a necessary step for the in-hospital product, which is being refined. We see this as an exciting area for DexCom to enter as we believe tight glycemic control will prove to be very important for hospitals – that said, there is significant competition on this front already. Overall, we think the new SEVEN has some vast improvements over the first-generation product - we are now wearing it continuously. In our opinion, reimbursement and some remaining reliability issues still stand in the way of broad customer demand, but while the reliability problems are fixable, we are

less sure about reimbursement, at least anytime soon. Nonetheless, we view Gregg's arrival as a very welcome signal on this front.

- **Becton, Dickinson 2Q07—Diabetes Care franchise moves forward with 7% growth:** During its July 26 earnings call, BD reported that its Diabetes Care franchise grew 7% globally to just under $175 million. Much of this growth was in sales abroad, where the Diabetes Care franchise grew 10.1%, increasing by $7.6 million to $82.8 million. BD's pen needle business remains strong – it's the leader globally, and during the quarter, sales were especially robust internationally (the company cited UK and Italy in particular). Particularly since Byetta has grown so much the last couple of years, the entry of LAR strikes us as a big worry for that franchise.
- **Bristol-Myers Squibb 2Q07—Dapagliflozin advances to phase 3:** There were no prepared remarks on the two diabetes drugs currently in co-development with AstraZeneca (saxagliptin, a DPP-4 inhibitor, and dapagliflozin, a SGLT-2 inhibitor) in BMS's July 26 earnings call run by CEO Jim Cornelius. Management said there would be a lot more detail on product development during an upcoming December 5 analyst call.. According to the company's press release, the partners have decided to move dapagliflozin into phase 3, based on phase 2 results. This was corroborated in AstraZeneca's earnings call. There's been little detail on the agreement with Pfizer, announced last quarter, on Pfizer's diabetes and obesity program. Pfizer is to cover research and early-stage development, while the companies will work jointly on phase 3 development and commercialization (Pfizer pays 60% and BMS pays 40%).
- **Eli Lilly 2Q07—Diabetes care shows robust growth:** Diabetes Care revenues (Humalog, Humulin, Byetta, Actos) for the second quarter totaled $775 million, up 13% versus $685 million a year ago. Humalog revenues came in at $358 million, up 12%. Lilly's share of Byetta revenue was $80 million (total Byetta sales were $152 million), up 54% versus $52 million a year ago and up 11% versus last quarter. While Lilly is clearly benefiting from Byetta, the company doesn't seem to be particularly aggressive about pushing Byetta into the market. We were surprised, for example, that there was no mention of the European rollout of Byetta during the call, even though Byetta has had EU approval for eight months. True, whether we're really moving toward a GLP-1-centric world is still an open question, but we find Lilly's apparent indifference in this area somewhat surprising, given the potential of the new class. Lilly did show some success in its goal of re-energizing its insulin franchise. Management said the company made gains in April, May, and June following two years of decline. Insulin market growth and pricing contributed to this quarter's growth, but neither can be sustained indefinitely, particularly not in this managed care environment. But we note that insulin growth this quarter represented about two-thirds of its diabetes franchise growth – definitely an uptick.
- **Amylin 2Q07—Byetta growth steady, INTO excites:** During its 2Q07 earnings call on July 24, Amylin reported $197 million in total revenues, up 15% over last quarter's $172 million result. Net product sales were $167 million, up 53% from $109 million in 2Q06. Symlin sales in 2Q07 were $15.2 million, up just under 33% from the same quarter last year and essentially flat with last quarter's $15.5 million. Byetta net product sales in 2Q07 were $152.1 million, $10 million less than expectations. Management had perfectly reasonable explanations – an inventory decline of a couple of days and some discounting – but we also suspect that Januvia prevented even higher Byetta sales. Amylin's best news, in our view, is that Byetta LAR appears to be marching toward approval. Though management appears highly attuned to all potential risks, none of the big ones – clinical, manufacturing, and most importantly safety – appear to represent major worries. We're excited to see large-scale clinical data on Symlin (pramlintide) for obesity, as the drug is the foundation of Amylin's

Integrated Neurohormonal Therapies for Obesity (INTO) platform. Also much anticipated in INTO, Amylin will be releasing data on a pramlintide plus leptin ("pramleptin") proof-of-concept study in 4Q07, as well as a data from a combo study with pramlintide, phentermine, and sibutramine for obesity. As Amylin's Dr. Alain Baron pointed out at ADA, pramlintide has the unique effect of restoring leptin sensitivity in diet-induced obese rats, producing synergistic weight loss when given in combination with the satiety peptide. The proof-of-concept study will show whether this effect translates to humans. We're interested as well in data on the triple combination of pramlintide, leptin, and PYY; Amylin has already finished a preliminary pramlintide plus PYY safety and tolerability study (results not yet released) in preparation for studying the triple combination in humans. Also in phase 1 is a second-generation amylinomimetic said to be ten times as potent and twice as effective as pramlintide for weight loss. Can you even imagine?

- **Merck 2Q07—Januvia franchise reports strong sales of $163 million:** On July 23 Merck reported very strong 2Q results for Januvia/Janumet. Januvia sales were $144 million, up 65% from $87 million the previous quarter. The drug is now approved in 51 countries and launched in 25. Janumet sold $24 million in its first quarter on the market; management noted that Janumet is expanding the Januvia franchise rather than cannibalizing from Januvia sales. Notably, managed care acceptance of these medicines has been strong and all major pharmacy benefit managers in the United States have added Januvia to their formularies. To date, 154 million covered lives have received tier 2 coverage for Januvia and 210 million combined have received tier 2 or 3 coverage – good work for the reimbursement team. In 2007, Merck added 112 million covered lives to tier 2 coverage and 132 million to tier 2 or 3 coverage. While most of Merck's success so far has been due to strong execution, particularly in the all-important PCP market, they have also clearly benefited from the bad luck of their competitors – i.e. Novartis' regulatory troubles and GSK's Avandia trauma – to say nothing about the rest of the industry's slowing drug development pipelines. On the pipeline front, management declined to talk about whether the rimonabant hearing has affected their CB-1 antagonist (MK-0364) phase 3 program – we can't imagine that it hasn't but overall in diabetes, Merck has clearly moved into a lead position.
- **Arena 2Q07—Gearing up for lorcaserin phase 3 safety review in September:** In the 2Q call on July 19, CEO Jack Leif provided updates on Arena's pipeline products including lorcaserin and APD668. The six-month data safety monitoring board (DSMB) review for the two-year, 3,200-patient BLOOM trial, the first of Arena's phase 3 trials for lorcaserin, will take place in September. As a reminder, the DSMB will look at rates of valvulopathy in treated vs. control patients and decide based on those data whether to stop or continue to trial. Valvulopathy is the FDA's primary concern for lorcaserin. Leif strongly hinted that he expects the lorcaserin program to go on and noted that the other two phase 3 trials should begin later this year. He asserted that the rimonabant panel decision does not affect Arena and acts only to thin the competitive landscape. However, we think it has set a precedent for much tougher reviews of obesity drugs, particularly CNS drugs like lorcaserin. APD668, Arena's GDIR agonist being developed by Ortho-McNeil, is in phase 1 trials with results to come "soon." Leif again noted that this molecule stimulates both insulin secretion from the beta cell and incretin secretion from the L- and K-cells in preclinical models, and in Q&A described the effect as 'analogous though not identical' to the effect of DPP-4 inhibitors. If this holds up in humans it could be quite promising, though we have yet to see clinical data confirming it. Analysts asked several questions about the effect of rimonabant on lorcaserin's safety review. Leif said that the blinded BLOOM data have not indicated any new safety signals beyond what was observed in phase 2 – in early trials the most common adverse events were headache, dizziness, and nausea. Leif also said that lorcaserin may be more effective than rimonabant, though we think it's difficult to make efficacy comparisons

between different trials. We imagine that Arena's potential partners will want to wait until the six month and twelve month DSMB reviews have been completed before entering into any agreements; Leif said it was possible that Arena would hold off on partnering until as late as the NDA date, which we assume is still set for 2009 if all goes well.

- **Roche 2Q07—Diabetes Care diagnostics franchise up 8%**: Roche reported July 19 that first half Diabetes Care sales grew 8% (6% in local currencies) to CHF 1.544 billion Swiss Francs ($1.28 billion US using an exchange rate of $0.832 per Franc), which Diagnostics CEO Severin Schwan characterized as above the overall market performance. This is an increase of 8% over CHF 1.428 billion in the first half of 2006 ($1.13 billion by last year's exchange rate of $0.79 per Franc). In American currency, Q2 sales were ~$656 million, up 10% from $595 million last year and up 5% sequentially from $626 million in the first quarter. Schwan said that Diabetes Care has recovered, primarily driven by sales in the US – first half sales growth in North America was 10% due to the renewed Accu-Chek portfolio. Roche's half-year report cited Accu-Chek Aviva, Accu-Chek Go, and Accu-Chek Compact as the main growth drivers. Blood glucose monitoring revenues rose 6% for 1H07 while insulin delivery sales grew by 17%. We estimate BGM revenues in the first half of 2007 to be about ~$1.19 billion, with second quarter sales of ~$610 million compared to $580 million in the first quarter and $550 million a year ago. Insulin delivery / insulin pump sales growth was down slightly from 21% growth in 1Q, though still impressive with first half sales of ~$97 million compared to ~$80 million in 1H06. Management noted that the new Accu-Check Spirit (launched in 4Q06) has sold well in the US and is being launched in a number of other countries as well. Schwan will be taking over as Roche CEO in March 2008.
- **Roche 2Q07—GLP-1 and DPP-4 inhibitor in phase 2; setback for glucokinase activator**: Pharma CEO Bill Burns's pipeline update in Roche's 2Q call showed no diabetes drugs in phase 3. However, Roche is working on several phase 2 and phase 1 candidates. First, the sustained formulations (weekly and biweekly) of its GLP-1 candidate R1583 remain in phase 2, which began in April 2007 and are currently recruiting in several countries. Burns implied that the efficacy of the molecule itself is strong, and the company is only working through formulation development for the extended release versions at this point. We think that the bad news on Novartis' vildagliptin (skin lesions, etc.), which will be delayed until 2009/2010, is good news for the GLP-1 class as a whole, though Roche's candidate is much earlier stage than liraglutide or Byetta LAR. Roche's DPP-4 inhibitor aleglitazar (R1439) was listed as planned for post-2010 submission on a pipeline side, though Burns didn't mention the molecule in his remarks. This is the first time we've heard the name for this candidate; last quarter R1439 was listed as phase 2 but without details as to the class of drug. As a reminder, Roche had previously killed DPP-4 inhibitor R1483, but it looks like it will continue pursuing the class with R1439. On a more negative note, Roche has discarded R1440, its phase 2 glucokinase activator (GKA), in favor of a backup molecule. Management cited "some associated toxicities" when investors asked about the molecule in Q&A, but emphasized that they don't think it's a class effect and that "there may be a way forward" with the backup molecule, which was in phase 1 but is now being moved toward phase 2. Lastly, Roche's CETP inhibitor for dyslipidemia, R1658, remains in phase 2 with a decision for phase 3 expected in the autumn. On the obesity front, first half global sales of orlistat (Xenical) were ~$282 million (CHF 339 million), down 8%. Xenical sales fell 6% in Europe and 17% in the US during 2Q compared to sales drops of 24% in Europe and 7% in the US during 1Q. This is the first year we've seen a downturn in Xenical sales (2006 full year sales were up 7%). Management didn't mention Xenical in the call, but we assume Rx sales will decline further in the US with the availability of GSK's over-the-counter (OTC) version of orlistat, Alli, which posted impressive sales of $157 million for its first quarter on market.

- **Pfizer 2Q07—Exubera billed as disappointing, with weak sales:** There was little discussion of Exubera during Pfizer's earnings call on July 18, with much more focus on Lipitor losing sales to generic statins. Exubera was called "disappointing" in both the prepared remarks and in the release, "despite positive feedback from users." By contrast, we hear very good things about the next-generation device from educators in particular who have seen it. Alas, worldwide Exubera revenue for the second quarter was $4 million. CEO Jeff Kindler promised to continue to execute the "2007 action plan," which includes DTC advertising: print ads began in mid-June this year, and TV ads began in late July. Pfizer promised to commit considerable resources to promising therapeutic areas including diabetes. It has a DPP-4 inhibitor in phase 2 (PF-734200), and an 11-beta-HSD inhibitor for obesity which seems also to be in phase 2 (CP-741952). A CB-1 receptor agonist for obesity is in phase 3 (CP-945598), which is also being looked at for type 2 diabetes – we're curious to see if and how this differs from rimonabant; we expect any company would have a hard time navigating the current regulatory environment.
- **Abbott 2Q07—ADC quarterly sales exceed $300 million for the first time**: Abbott Diabetes Care reported July 18 that 2Q07 sales reached $308 million, up 6.3% from a year ago and up 8.1% sequentially from the first quarter. In the US, sales rose just 1.6% year-over-year to $142 million, or 2.2% sequentially. Internationally, sales increased a more robust 10.7% year-over-year to $166 million due to the positive exchange rate of 7.1% (without the exchange impact, the increase would have been 3.6%). Management said it anticipated accelerating growth for Diabetes Care in the third quarter, led by the launch of FreeStyle Lite (billed as a new meter that does not require coding but retains the accuracy of the FreeStyle platform) and the launch of other new products. We note that neither Roche nor LifeScan offer devices that auto-calibrate, though Bayer of course does. Bayer has done very well as the pioneer of this no-coding feature, which has been very popular among CDEs in particular. There was no mention of the smaller, faster Titan meter, but we assume that it will still be launched in 2H07. Management had said in the 1Q07 call that it expected a return to double-digit growth in 2H07 so we'll be watching for an uptick. Navigator remains under "active" FDA review. The June European CE approval for Navigator was mentioned, though no details were given on the European launch. Management reminded that Abbott's integrated blood glucose monitoring system remains in development – this would combine a meter, test strips, and lancing capabilities in one device, which management said would enable simple point-and-click testing – still no new information from last quarter. Prior to TheraSense, Abbott had the Sof-Tact for this purpose, so we assume the second generation will be much smarter. On the pharma side, there was no mention of Meridia or anything on Kos inhaled insulin. We understand that the inhaled insulin product is in phase 2 development. We aren't surprised this wasn't discussed given Pfizer's very disappointing sales of Exubera.
- **J&J 2Q07—LifeScan and Animas both up double digits in strong quarter**: J&J's July 17 earnings call reflected real strength at LifeScan – this was great to see after slower growth in recent quarters. LifeScan revenues came in at $596 million globally, up 11% year over year (up 14% excluding currency impact). US sales of $310 million rose 7%, and international sales of $286 million increased 16% operationally (23% excluding currency effects). This was a welcome lift for US sales, compared to flat year-over-year growth last quarter – it's also a strong result given a tough comparison a year ago, when US growth was 14%. Although the company didn't mention it, according to our model, these results are records for both US and international sales, and the US result in particular is the first result over $300 million for LifeScan. CFO Dominic Caruso pointed to the UltraMini and Ultra strips as sources of strength. We can corroborate that UltraMini marketing was strong at the July Children With Diabetes conference; a page was taken from Apple's book, as LifeScan has really lifted the UltraMini vibe with colors in hot pink, silver, and black, among others.

Importantly, though Animas growth wasn't reported, Caruso did mention that Animas increased double-digits over a year earlier – this is the closest we have come to understanding the growth of Animas though of course we don't know whether that was a tough or easy comparison as we have no "year ago" revenue information. LifeScan was called one of several primary contributors to total operational growth of the company – this is largely due to international strength, on which there were no specifics.

- **Novartis 2Q07—Galvus FDA resubmission expected mid-2009**: There was little mention of Galvus in the prepared remarks of the earnings call on July 17 beyond a terse scripted update from pharma head Thomas Eberling, in which he noted that Novartis met on April 27 with the FDA and submitted a protocol for an additional trial in June, with FDA feedback expected at the end of August 2007. Management clarified in Q&A that the FDA asked for a trial in renal impairment patients because skin lesions were observed at 5x the dose in primate studies – and much more damning, at 4-6x the therapeutic dose in normal human volunteers. The FDA was concerned that the drug might get up to that dose in 'susceptible' patients – i.e. renal impairment patients. We note that in contrast to Januvia, Galvus is actually hydrolyzed before it is cleared by the kidneys so there should theoretically be less risk of dose accumulation in renal impairment patients than with Januvia, but the FDA is no doubt being as cautious as possible. The proposed trial is a six-month study with 'several hundred' patients; the FDA will give feedback on trial design in late August, but if it approves, the trial will begin in 4Q07 and finish in late 2008 with FDA resubmission expected in mid-2009.

  Management would not speculate on whether the FDA will require renal impairment studies for all DPP-4 inhibitors, but commented that these same skin effects have been seen with other molecules. No word on whether they have been seen with Januvia. When asked what would differentiate Galvus from the rest of the DPP-4 inhibitor pack considering the late expected launch date in 2010, management pointed to efficacy data, especially relative to TZDs. We're not sure how valid any efficacy comparisons are without head-to-head data. We view this as a positive for Amylin's Byetta and a positive for Merck's Januvia – positive for Merck because it confirms that Galvus will not reach market until at least late 2009, although offset by at least a slight negative because it suggests that the skin lesions may be a class effect, or at least may be common to the DPP-4 inhibitor class. On the other hand, a recent *JAMA* meta-analysis on incretins didn't raise skin lesions at all; it only pointed out that DPP-4 inhibitors are associated with higher rates of nasopharyngitis (6.6% vs. 6.1%), urinary track infections (3.2% vs. 2.4%), and headaches (5.1% vs. 3.9%). Additionally, Merck's Janumet was approved after these issues surfaced, also an apparent positive. If the skin lesions really are a class effect, it may be that the reason we haven't heard any reports with Januvia is that in normal clinical use, these drugs simply never reach the dose levels necessary to cause skin lesions. Certainly the possibility is concerning though in the near term, Merck is marketing more to PCPs, and we believe this group is less concerned overall than endos. No news on GALIANT, the head to head TZD trial.

- **BodyTel—Developing GlucoTel, a glucose meter with Bluetooth technology:** BodyTel Scientific Inc., which specializes in wireless healthcare products, plans to submit a 510(k) application to the FDA for GlucoTel, its blood glucose meter, in the fall. BodyTel hopes to bring the device to US market in late 2008. BodyTel bills the GlucoTel meter as unique because it has built-in Bluetooth wireless technology, although in fact Agamatrix's Jazz meter also has Bluetooth (see our Agamatrix update above). GlucoTel meter results would be transferred via Bluetooth to a wireless application running on the patient's Java-enabled cell phone. The phone then transmits the results to a GlucoTel database, where they can instantaneously be read by the patient's doctor, or anyone else the patient authorizes to receive results. BodyTel would also allow people with viewing authorization to customize

alerts (e-mail or text message) for high or low readings. CEO Stefan Schraps said the primary purpose of this device was to increase patient compliance by giving physicians access to more accurate data without burdening the patient with logbooks or manual data synchronization. We view the GlucoTel system as a logical extension of glucose monitoring. However, it remains to be seen how easy the system is to set up and whether it works as easily as advertised. For patients, the system promises simplification and automation. And for doctors, this system could bring compliance, compliance, compliance. No more faked results or blank logbooks. As we all know, compliance is often the greatest challenge of all.

—by Kaku Armah, Daniel Belkin, Michael Chen, Jenny Jin, Mark Yarchoan, and Kelly Close

4. Renowned Self-Help Guru Stephen Covey Takes Aim at Diabetes at AADE

Dr. Stephen R. Covey comes to diabetes highly commended. An international authority on leadership, family, and organizational values, Covey is perhaps best known for his self-help book, *The 7 Habits of Highly Effective People,* which has sold more than 20 million copies in 20 languages. In 1996 *Time* magazine named him one of the 25 most influential Americans, and his awards range from International Man of Peace to National Fatherhood Award.

Several years ago, Covey's wife was diagnosed with type 2 diabetes. Sandra, who is now 70, has had her challenges, including a knee replacement, but she eats prudently, exercises regularly, and keeps a "scoreboard" of her daily blood sugar numbers. "She's had some ups and downs," Covey told us, "but she keeps the scoreboard and she knows exactly where [her blood sugar] is. I'm very proud of her."

The 74-year-old Covey is not necessarily a health expert (he has an MBA from Harvard and a doctorate from Brigham Young), and, frankly, he's not an expert on diabetes. He didn't know what medication his wife took and had never heard of an A1c test. As such, he was not planning to write about diabetes. But he was approached by Bayer Diabetes Care to do just that and in collaboration with the American Association of Diabetes Educators (AADE), Covey has written *"The 7 Habits of Highly Effective People with Diabetes*."

The brochure also includes AADE 's own seven self-care behaviors, which it introduced several years ago, plus an "Action Plan" that stresses easy-to-achieve self-care goals. "Remember to aim for progress, not perfection." Bayer distributed the pamphlet at its exhibit at the AADE meeting in St. Louis (see our highlights below), where Covey also gave the closing talk of the conference. We think Bayer made a great call on this; the pamphlet was one of the best giveaways that we saw in the exhibit hall.

Covey said that his seven habits for highly effective diabetic patients were derived from the same habits that he identified for successful people in his first book. As he pointed out, these habits are universal, and indeed most of them will look familiar to anyone versed in the literature of diabetes education: being proactive, having a clear goal, achieving small goals first, etc. But Covey says this approach works because "it's a sequential framework; that's the key." You can track your progress, measure your successes, and stay motivated, he says. Also important is working with others who will hold you accountable and help you achieve your goals.

We suspect that such guidance has been offered, in rough terms, by others over the years, but Covey's track record suggests that he has a way of framing issues that hits home and gets results. We hope that this is just the beginning of his involvement in diabetes – whether he is motivated by his wife or humanitarianism, we hope he will stay involved, speak out often on the subject, and help find new and better ways to motivate and inspire patients.

"The key to life is to serve other people – that is the source of true happiness, not pleasure," Covey told *Diabetes Close Up*.

So for now, we'll believe that better things are around the corner – or, to use Covey's wonderful phrase: "Live life in crescendo."

7 Habits of Highly Effective People with Diabetes

- Be Proactive. Choose your actions and take responsibility for them.
- Begin with the End in Mind. Create a vision for you life, based on what is more important to you.
- Put First Things First. Prioritize your tasks based on what is truly important.
- Think Win-Win. Build strong relationships with others by helping them succeed as well.
- Think First to Understand, then to be Understood. Listen with your mind and heart, then make yourself understand.
- Synergize. Build relationships with others to help you make progress in every area in life.
- Sharpen the Saw. Keep all parts of yourself sharp: physical, mental, social, and spiritual.

—by James S. Hirsch and Kelly Close

5. AADE Highlights, August 1-4, St. Louis, MO; www.diabeteseducator.org

The American Association of Diabetes Educators (AADE) meeting is one of our favorite conferences to attend every year, not least because it brings together thousands of the most clinically-focused individuals involved in diabetes care across the United States. More than 4,000 diabetes educators, nurses, pharmacists, dieticians, and others came together in historic St. Louis this year to attend the many wonderful symposia, workshops, and social events. We learned a great deal from the sessions we attended with these experts as well as from our AADE survey, now in its second year, which helped us gauge what the clinicians out in the field are really thinking about the latest trends in diabetes – for example, that devices are hot and Avandia is not. See below for a summary of our learnings!

- **CDEs were very interested in CGM, reinforcing what we saw at ADA**. There were many talks on the technology and quite a lot of interest at the booths. In many cases, the CDEs we talked to rated the technology very highly even though they hadn't had any experience with it. We believe that lack of reimbursement for CGM continues to be the single greatest obstacle for its wider adoption, an opinion reflected in DexCom's low revenue for the second quarter. The results of STAR3 and the JDRF trial will be extremely important in obtaining reimbursement.
- **Despite the hype about new technology and drugs, simplicity is the real key**. Treatment is getting more complex and that's overburdening CDEs. Add to that the fact that there aren't enough CDEs (or endos), and we have a real need for simple drugs that don't require a lot of education. This is why we think Januvia has been so successful, not just with PCPs, but with specialists as well. A talk on treatment adherence reinforced this message; the simpler the treatment regimen, the more likely the patient will follow it.
- **On that note, Merck is executing extremely well with Januvia**. Januvia is clearly doing very well, and we suspect that its simplicity and tolerability will make it as surely a part of the specialist's toolbox as the PCP's, barring any safety issues. Notably, while the Amylin booth attracted a steady stream of CDEs throughout the conference, as well as large audiences for the Davida Kruger and Nicole Johnson talks, most of the activity in the Merck

booth seemed to revolve around the giveaways. We think this speaks to the simplicity of Januvia and Janumet… there simply isn't very much to ask about these drugs.

- **Inhaled insulin isn't dead, but this iteration may well be**. The Pfizer booth was largely abandoned and the inhaled insulin talks throughout the meeting generated little attendance. Nonetheless, most of the CDEs we talked to were quite emphatic that inhaled insulin isn't dead. They seemed to think that a lot could still be done with it. Almost no one had had any patients actually use Exubera, however. It sounds like neither patients nor CDEs are excited about the technology, but at the same time we noticed that the CDEs we talked to really like the idea of choice (just like patients) and wanted as many options as possible… even if they didn't have any good candidates for inhaled insulin at the moment.
- **On why patients aren't achieving the target level of glycemic control…** We heard the same explanations reiterated in several symposia: under-use of insulin, inappropriate use and titration of medications, lifestyle management challenges, and a lack of understanding of therapeutic options. There are several additional barriers to injectable medications: patients often have negative attitudes or fears about injectables; many consider injectable medication a "punishment" that is given only after they have failed on their oral medications.
- **CDEs aren't particularly aware of what's coming down the pipeline**. We were surprised to find out at the Merck-sponsored symposium that many of the audience members hadn't heard of Byetta LAR. This ties into the overarching theme we picked out – that CDEs are more overworked than ever and the amount of education they can supply is vastly outstripped by demands on their time. There was hardly any whisper of rimonabant or vildagliptin at this meeting, though there was one session on the former and a few references to the latter in incretin talks.
- **On whether Actos and Avandia increase cardiovascular risk…** So the first thing about this is that GSK did not exhibit at AADE, so there was no Avandia anywhere. This pretty much shocked us. There was, as you would expect, a lot of discussion about Avandia but not much consensus. In our discussions with CDEs, we heard mixed answers about whether Avandia is dead. Several mentioned Takeda favorably because it gives out a lot of samples with virtually no follow up. Few CDEs said that they would point-blank stop prescribing Avandia, but we sensed a lot of caution. As one CDE pointed out, "If you have two drugs that do the same thing and there's problems with one of them, then why would you use that one?" Anecdotally, we also heard some CDEs say that Actos causes less edema and weight gain, but we're not sure if this observation simply came out of the current negative scrutiny against Avandia. Dr. Om Ganda, a highly-regarded cardiologist from Harvard, briefly addressed the "burning question" about whether Actos and Avandia differ regarding CV risk in the Takeda evening symposium. The audience seemed like it wanted a more concrete answer than what it got: it depends on data to come. He suggested that if there is a cardiovascular difference between the TZDs, it could be due to their different effects on lipids (LDL, HDL, and TG). He also pointed out that PROactive suggested that pioglitazone reduces MI (we note this was suggestive but not statistically significant), whereas it looks like Avandia doesn't decrease CV risk and may well increase it… but, the July 30 expert panel clearly thought there wasn't enough evidence to take Avandia off the market. The best thing to do, he said, is to remain careful about patients with CHF. We thought this was an interesting choice of words: "remain careful" – since we think a lot of the time diabetes patients are on drugs like Avandia despite having cardiovascular issues.

—by Kaku Armah, Daniel Belkin, Michael Chen, John Close, Jenny Jin, Mark Yarchoan, and Kelly Close

6. DCU Interview with Jeff Hitchcock – Inspires, Inspiring

Below are some highlights from our interview with Jeff Hitchcock, creator of Children With Diabetes (CWD), an online community for parents, kids, adults, and families living with type 1 diabetes. Since its inception in 1995, the site has grown to become one of the largest diabetes web sites, with over 20,000 visitors per day. Here, Mr. Hitchcock discusses the history of CWD and his own struggles caring for his daughter Marissa, who was diagnosed with type 1 diabetes at the age of two. The entire interview is available on the lower left hand corner of the Diabetes Close Up website at www.closeconcerns.com.

Jim Hirsch: When was Marissa diagnosed with diabetes? What was the hardest part for her?

Jeff Hitchcock: Marissa was diagnosed when she was just 24 months old, in September 1989. It was a long time ago, and the tools used to manage diabetes then were certainly crude by today's standards. Lancets were, as I tell people, the size of fork tines. And meters took 120 seconds with a gigantic drop of blood.

I guess the biggest challenge we faced was trying to reconcile a toddler's normal eating behaviors with the action of insulin. A smart child quickly determines that food is a powerful manipulative tool, and if you sit down for dinner and give X and Y and they say I'm not eating, mom and dad get rather anxious.

Jim: Sounds like our house. And this brings us to how Children With Diabetes (CWD) came into existence…

Jeff: For many years after she was diagnosed, I worked in the high-tech software industry. There was one forum in particular on the old CompuServe forums about diabetes. The postings on there dealt primarily with adults who had diabetes (the number of people who had online access was very small back then - this is way before the Internet). There was nothing there to help parents and absolutely nothing for kids.

In the fall of 1994, I was in a company that got access to the Internet. It was clear to me that this medium was the perfect place to build a support environment for kids who had diabetes. At the time, there were a couple of sites online. The biggest was called the diabetes knowledgebase run out of the University of Wisconsin, Madison. And again, the content was adults with diabetes, both type 1 and type 2. Nothing for parents.

As luck would have it, I found myself laid off in the summer of 1995 and came home. I called my Internet service provider and said I'm launching this site today; I need a full time modem connection. CWD launched the day I got laid off, with a page about Marissa and some wacky graphics. And I had no real thoughts on what it would become.

Kelly Close: At that point, how many people had you communicated with who had children with diabetes?

Jeff: None that I recall, to be quite honest. There was nothing there for families who had kids with diabetes. CWD was sort of my attempt to pass on the philosophy of my wife and me, which was really to live your life and fit diabetes into it, not the other way around.

Jim: Going back to the foundation of the organization, how did it evolve as you got your feet wet?

Jeff: I made some overtures to companies like LifeScan and was told, "The Internet – that's pornography. We don't want to be there." There was no financial support.

I did receive a contract from the JDF, as JDRF was called at the time, to build and host their initial website, which was called jdfcure.com. That lasted about 18 months before they took it in-house or moved it or something.

But back then, the Internet was very new. One of the things that helped us is someone at Yahoo discovered the site and featured us in a "what's new" page. Once that happened, our traffic began to just grow and grow and grow and grow.

And the growth has not stopped.

Kelly: What it was like having people writing directly to you?

Jeff: CWD has always been free and anonymous. That has been one of the things I've always wanted. In maybe late summer – like October-ish – I probably got the first email to "Dear Dr. Hitchcock, please tell me about my insulin." About that same time, a guy named William Quick who is an endocrinologist in Kansas City ran a site called Diabetes Monitor, which still exists. His Internet service provider was having problems keeping his site up. So I asked him if he would answer these questions in exchange for me hosting and keeping his site up, and he agreed. And that served as the foundation for what is now the "Ask the Diabetes Team" part of the site.

Jim: Were you still thinking at that point that this could be a business?

Jeff: No. At that time, having been told that no companies wanted to be online, from a sponsorship perspective, I had no delusions that this was going to be anything other than a hobby. It remained that until – I'm not even sure. If you go basically to late 1999, CWD was not bringing in any financial support to speak of. And it was to the point where I almost wanted to just turn it off because it was so time-consuming.

It was in the fall of 1999, when people were investing a lot in the Internet, and Internet health in particular, that myself and two other people created Diabetes 123, our company, and took over running the website from what was the CWD Foundation, which is now a separate entity. We then promptly watched the NASDAQ crash. So that was another very scary year. Another "go a long time and not get paid" kind of thing.

Jim: Did you quit your job?

Jeff: I walked away from what was a very nice job thinking that this was an easy business. You've got to kind of go back to the 1999 mentality and what we all thought was possible. Some of the things we had thought about doing just did not make sense in retrospect. Online diabetes education is a very expensive endeavor from an infrastructure perspective, and online sales of diabetes-related products have become something that the Wal-Marts and the Walgreens manage, not the small boutique companies.

But the other thing that happened in 2000 was that Laura Billetdeaux, a mom on our parents list, sent a note out to that list and said, "Who wants to come share a vacation in Orlando?" This became the first official CWD event in June of 2000. With her email to 600 families, 110 families responded and 550 people showed up in Orlando. It became clear to us that conferences were something that people wanted.

Kelly: Was that the first time that the companies had kind of reached out?

Jeff: We had some financial support from LifeScan. I think that came about 1997 to fund a section of the site about camps. But that was pretty much it. There were a couple of little companies. Not enough to pay a mortgage and all that kind of stuff. And Laura made a call.

When it became clear that it wasn't just five families going to show up at Disney, that this was a serious thing, she began calling various diabetes companies. TheraSense stepped up

and was the first company to provide financial support for a CWD event. This was prior to them actually having a product on the market.

They took a leap of faith in us that this was going to be something that was both worthwhile and would obviously be beneficial from a corporate perspective. You want them to feel that. But it was really a big leap of faith in us; that this sort of ragtag group of Internet people was going to do something.

After spending a day at Sea World and a day at the Magic Kingdom, we asked the families what they wanted, and we scratched our heads and said this is really something that could be something. And the feedback was that people wanted real conference kinds of stuff. These were parents who had gone to trade shows and conferences and such as part of their regular work, and they knew what these things could be. From that came the format for Friends for Life as we know it now – educational sessions, focus groups, a lot of social activities.

Jim: What do you think the biggest problems are, either from a parent's or a patient's perspective, in diabetes?

Jeff: I don't know that there's a one biggest issue. I think a family's struggle with suboptimal care; going to clinicians – whether it's a diabetes practice or a general practitioner – who don't keep up or aren't aware of the latest management tools and strategies, and who impose purely artificial barriers to adoption of new tools, such as pumps.

Nothing is more frustrating than hearing a parent say, "My doctor won't prescribe a pump until my teenager's blood sugars are perfect." They may not be able to achieve those goals without that pump – those are the kinds of frustrations I see.

So part of what we try to accomplish is to let families know what the latest in management strategies and tools are. There is no one solution for everybody. Part of this is just seeing what science tells us works. What are the good strategies? And letting families optimize care based on their personal situation.

Jim: What do you think are the biggest misconceptions among parents and patients?

Jeff: I'll give you an example that just came up in the last couple of days on our forums. A dad posted about his son being newly diagnosed and was very anxious about the long-term effects of type 1. He was just very worried that his son, who is now 16 and literally just diagnosed five days ago, is going to suffer what his aunt did 20 years ago.

I think there's this enormous misperception about type 1 versus type 2 in the general population, and a lack of appreciation for the dramatic advances that medicine has made in caring for type 1 diabetes in the last 10 or 20 years. I think that people new to this, and who aren't left with a good diagnosis experience, leave feeling really anxious and depressed when I don't think they need to be.

Jim: Which companies impress you the most?

Jeff: Well, I don't want to be in the position of showing favoritism to any particular companies. When I look back on almost 18 years of living as a parent of a child with diabetes, and I look at the institutions or organizations that have made the biggest impact on my daughter's life, it has been industry.

When we compare glucose monitors from 1989 to today, we go from the best meter on the market that took 120 seconds and a drop of blood that would have made a bricklayer cry, to meters today that are in the three- to five-second range, with sub-microliter volumes. And integrated data management or connections to computers to help identify patterns and improve management strategies.

We look at insulins – regular and NPH was the norm, and now both short-acting and long-acting analogs have given us incredible dosing options and much better predictability. They reduce hypoglycemia, which has always been the limiting factor on optimizing control.

And insulin pumps, which in 1989 were available but really were not something you would have put on a two-year-old, are now so small and so lightweight that you can put them on toddlers. And those tools are what have made that nephropathy study a reality. These tools make living with diabetes easier. And they've given patients the opportunity to basically have complications be something that they don't need to worry about like they used to.

Jim: What message can we send to industry about what they need to do to make diabetes care better?

Jeff: Well, we certainly see, obviously, a lot of investment and research in continuous sensing. And I think it goes without saying, based on a fair amount of DirecNet and other studies on continuous sensors that that is the next quantum leap in the hardware that we use to manage diabetes. The opportunity to see, in real time, what your blood sugars are doing will, in my opinion, change the world in ways similar to home glucose monitoring.

The science may not be enough to convince payers that this is something that they need to reimburse, but I think it's getting there. Anyway, getting coverage for sensors, for all sensors that are available, and for kids and adults, is important. That's reported often on our forums and on our chat rooms.

While we're waiting for universal coverage, we're seeing more and more better options: families catching glycemic loads at night, families being able to sleep because they have something that they can rely on to alarm in the event of a pending hypoglycemic event. From a parental perspective, that is what we worry about. I'm a lot less worried about a high blood sugar than I am about a low that can result in a seizure in the middle of the night.

From an industry perspective, I don't know that I'm asking for them to cure diabetes. I see a real cure coming from academia. From places like the DRI and the NIH and the scientists who are looking for an intervention on an immunological basis. After all, this is an autoimmune disease. Just pouring more islets into the body, however you protect them, I don't know that that's the real answer. I think the answer will eventually come with an immunomodulatory therapy.

Again, that's just my opinion. There may be lots of ways to solve it biologically, but in the end, it is an autoimmune disease. I look for industry to find better ways to live on a day-to-day basis. And they are doing that with audible sensors, with better pumps, with better blood sugar or glucose measuring devices, whether through blood or interstitial space.

Jim: Which companies have been most helpful in helping you run Children With Diabetes?

Jeff: There are a number of companies that support what we do, both online and at the conferences. You can see them just by visiting the Web site and seeing who has a presence, and who has a presence at our conferences. And they are very generous in their support. They believe in helping families to live better lives. And I think in the end, that's just good for business.

Jim: Jeff Doug Burns was arrested for hypoglycemia in a movie theater a while ago. He blogs a lot about diabetes and said, "It seems the medical profession and the diabetes industry is more interested in marginalizing the risks inherent with insulin replacement therapy rather than owning up to them. For decades, hypoglycemia has been routinely blamed on patient error rather than the non-physiologic manner in which it is dosed. We have been told that

education is the key. And yet, in spite of the significant increase in patient education, the incidence of ER visits due to insulin-induced hypoglycemia stands at record levels."

And then he says, "It's even worse at most large diabetes conferences. Health care professionals are inundated with information about more accurate and simpler blood glucose monitors and insulin-delivery systems; yet nonprofit advocates for curing diabetes, or other charitable organizations, are woefully underrepresented, a place on the periphery of the exhibition halls." He could be talking about Children With Diabetes.

He says, "The theme reinforces the prevailing belief that diabetic disabilities and their associated economic costs are caused by people with diabetes, not by their disease."

Jeff: Let me see if I can touch on a couple of those things. We, as parents, certainly do not underplay the risks of hypoglycemia. That is, without question, what keeps us up at night, literally and figuratively, as I had mentioned earlier.

When we polled our audience on how many people check their kids at night, it is a significant number, well over half. I think about a third are checking their children every single night in the middle of the night. And we do that because brain damage is not acceptable. It's just not – you have a brief period of time to keep your kids healthy. You've got 18 years before they head off to college. So we do whatever it takes.

Do I think industry downplays that? No. I think this is something that we all understand. It requires… education, which may be the word that your blogger doesn't like, but that's what this is about. You learn how exercise affects your blood sugar; you look at foods, you look at carb-counting. You use the tools to measure glucose to give you the data, and I think that's why these continuous sensors have such a great opportunity to help reduce the incidence of these low blood sugar events, which are the limiting factor in control.

Do I expect industry to step up and do more? I don't know what more we can ask of them. We want these companies to build better tools. I think it is unfair to expect a corporation to cure a disease. That is not what they are about. They are about building products and making money, and that is simply what they are. And I think people who expect them to cure diabetes have misplaced expectations.

Jim: How would you characterize research funding for a diabetes cure?

Jeff: The amount of money that's funding [Type-1, cure-related research] is going to be directly related to how vocal groups are in Washington to fund that or how willing people are to donate to walks and "For the Cure" type of things that both the ADA and JDRF and other organizations run.

The big funder though, of course, is the NIH. And if people want more funding to come from the federal government, we know how to do that. You lobby. You write your representative. You make it known that this is important. And I don't know that the diabetes community has as effective a lobbying organization as other disease states, such as AIDS and breast cancer.

Jim: Why do you think that is?

Jeff: I don't know. Some of it may be related to the fact that type 2 diabetes is sometimes viewed as something that is the fault of the person who has the illness. There is still a lot of that mentality. And I think that as science teaches us more, we will come to see that this is not just a lack-of-willpower problem, but that there is a lot, physiologically, going on that we simply did not understand.

And perhaps then this "you did it to yourself" mentality will be pushed aside and the medical community and the nation will realize that diabetes is the biggest healthcare issue we have to

deal with, and the resources needed will be allocated. A lot of resources now are going into type 2 related work, not type 1. Organizations that try to blur the two, I think, are often a little disingenuous.

Kelly: Can you talk about what product out there is doing really well with customers, and what makes it such a good product. Is it price? Is it that they've got a great education program? Is it that they like the color?

Jeff: I think the biggest deciding factor on products is customer service. If you look at insulin pumps, for example, that's a big cash outlay no matter how you cover it; a lot of supplies every month. And, effectively, you've entered into a relationship with a company, because most people buy their supplies from their insulin pump company. People talk about what happens when things break. Insulin pumps are mechanical devices, and like any mechanical device, some number are going to break or have a failure. And it's more how the insulin pump company responds to those episodes of crisis – because a pump failure is always a crisis – that determines how patients and future customers will view that company. People don't complain so much about the fact that their pump broke. They complain about the fact that their pump broke and they didn't get a replacement for three days because their rep was out of town… and the company didn't think they were important enough to make a delivery that night. That's where a little investment goes a long way.

Jim: What would you say for meters? Because meters typically don't break down, what's the deciding factor there for patients, in your judgment?

Jeff: For our audience – parents who have kids with diabetes – having a second meter that you don't have to go buy, so that you can leave one at school and have one at home, is a big thing. So a meter company that will accept a phone call to their customer service where Mom says, "Tommy is in school. Can you send me another meter – this is what he uses – so that we don't have to keep schlepping it back and forth?" Then they send it out, and it arrives the next day… that's what they should be doing.

Jim: Do the parents expect that meter to be free?

Jeff: Absolutely. It's a small cost to that company, but it demonstrates a real appreciation for what that family is going through and a need that needs to be met. The company that willingly says, "Not a problem. What's your address? It'll be in tomorrow's mail," is the one that has a customer for a very long time, because they've seen that they matter to the company.

Jim: I guess that would probably hold true for adults as well. Kelly and I schlep our meters everywhere. We lose them. And we need multiple meters for the multiple venues that we're in each day.

Jeff: Of course. Well, if you're an adult with type 1, you want one at home; you want one in your car; you want one at the office. That just sort of goes without saying.

Jim: But what's interesting is I'm not aware of any company that has figured that out and says, "Buy this meter, and we'll give you a second one free."

Jeff: Maybe a 2-for-1 deal on retail would be good.

Jim: So what about insulin? Is it just a commodity product, or do people care whether they have Humalog or Novolog?

Jeff: I don't know the answer for that. And some of that is really about what the science tells us. When people started using analogs and pumps, there were anecdotal reports of one insulin working and the other not. And the scientists pretty much said they are equivalent. From the families that report one insulin working better than another, it may simply be that their body

has antibodies to that particular insulin formulation, or they have some sensitivity to non-insulin components in that drug that make a difference in how long a set lasts. I don't know that science has an answer for that one. So some of the choice on that may simply be what their particular co-pay covers best, or for families who come to Friends for Life, they see who is there and who is not.

Jim: Or what the doctor prescribes.

Jeff: And a lot of it can be just that. We all know that families leave a diagnosis experience or an office visit with whatever the healthcare team provides. And there is inertia to continue to use that.

Jim: Do you see that changing over time? It does seem like more of the companies are trying to reach the patients directly.

Jeff: There is no question that's changed. And you just have to look at the television to see all of the commercials for meters. The message adds things that matter to the patient, not to the clinician: it's painless, or it doesn't require coding; or the things that make a difference to the family. So it's very obvious that there is more direct-to-consumer marketing in the glucose meter space.

Jim: What impact do you think that's actually had on the companies themselves?

Jeff: I have no idea. But I think it's a good thing if it raises the awareness that there are multiple tools. It's not just whatever you left the doctor's office with three years ago. You should be aware that there is innovation. And if it does nothing other than get someone to go and ask either the pharmacist, or their doctor, or somebody online what's out there now, they may find a tool that's better for them. But it does sort of put some pressure on companies to continue to innovate and come out with new models.

Jim: What's been most satisfying about what you have built over these years?

Jeff: When I sit here and look online at the traffic statistics, they've gone up consistently. But those are just numbers, and it's difficult to have an emotional experience with that pool of data. But when I'm standing onstage in front of 1,500 people and watching a slideshow of our kids over the years, growing up healthy and happy, and interacting at conferences and the like, that is very rewarding. It can't not be. So while the website, obviously, has a chance to reach many more people than our conferences can, the conferences have become the heart and soul of what we do.

Jim: And the company itself remains you and Laura?

Jeff: We're the two employees. But I do have contractors and what not, and a couple who helped with online stuff, and then an enormous number of extremely dedicated volunteers at the conferences who do everything from pre-conference security to the different groups who take on the childcare or who run registration and make sure all the packets are stuffed. It's a lot of work. And without those volunteers, it would never happen.

Jim: What frustrates you or concerns you the most about diabetes today? You've spoken about how much things have improved, but there must be things that still get you frustrated.

Jeff: I think a very significant, unaddressed problem is access to these tools. And that gets to how we fund healthcare in the US. And, at some point – and I don't know how soon – as a nation, I think we have to realize that access to what we know to be good healthcare practices, whether it's in diabetes or cardiac health or anything, makes a difference for us as a nation, both economically and otherwise.

It's foolish in my mind that companies like General Motors have to worry as much about health insurance as they do about the quality and features in their automobiles. Those companies should be building cars or computers or whatever they do. And, as a nation, I think we need to step up and realize that healthcare matters as a nation, and we're just not there yet.

Jim: So, when did CWD in effect become your full-time job?

Jeff: I think sometime in 2002. We finally had enough both online support and sponsorship at the conferences that I could put aside the separate job. Of course, a deciding factor was health insurance. We were able to get a policy. It's basically a group policy with two families, my family's and Laura's. Without that, it would have been very difficult to do this.

Again, that demonstrates that we have to find a way as a nation to solve access to healthcare to ensure that small businesses or entrepreneurs, or people who have new ideas that can make a difference, have an opportunity to try that out and succeed in our country, not some other country.

Jim: Do you envision ways of expanding what you've already got, or are you kind of getting ready to wrap things up and retire? [Laughs.]

Jeff: I can't retire until we have scheduled the Children Who Used to Have Diabetes Conference. We're not there yet, though I do look forward to that. I think that from the web perspective there are a lot of things that we could be doing that we're not. And I certainly have plans to do more content-related things. There's no sense disclosing what those are. But there's a lot of opportunity, both online and in the conference space. I don't know that we're going to do a whole lot more conferences per year in the US, but I do believe that we have an opportunity to take what we do outside the country to other places. We have our first non-US conference scheduled in Toronto later this year. I think that in the next couple of years you'll see us in other places as well. Again, it depends upon finding the financial support from the companies that make it possible.

Kelly: It is really inspiring what you've done and the energy that you have behind you in all of the volunteers and so forth.

Jeff: I think I passed on to Kelly the real dedication that we had last year. A mom had a young daughter with diabetes, and she was pregnant with another baby. And she scheduled her C-section two weeks before Friends for Life so that she would be well enough, and the baby would be old enough, so they could come.

Kelly: That says it all … thank you so much Jeff, to you and Laura and the host of contractors and volunteers that make CWD what it is. It's been an honor to speak with you.

—by James S. Hirsch and Kelly L. Close

7. *JAMA* on STAR1 results: "Poor patient adherence may undermine aim of continuous glucose monitoring"

While problems with device calibration and lack of rigorous trial data are barriers to proving the efficacy of CGM, an additional barrier is patient adherence. This is the key takeaway of a news piece by Mitka, M. et al. published on August 8 in the Journal of the American Medical Association (JAMA)*, which addresses the STAR1 continuous glucose monitoring (CGM) results presented at ADA in June 2007 in Chicago.*

- **The article first highlights the methods and findings of the STAR 1 trial** and a subset analysis by Dr. Irl Hirsch of the results:
    - The six-month multi-center trial split 138 experienced insulin pump users into two groups: the CGM group or the conventional fingerstick group.
    - All subjects had initial A1c levels above 7.5% before the trial. A1c levels for both groups decreased from a mean of about 8.5% to 7.8%.
    - Dr. Hirsch and colleagues found a linear relationship between CGM compliance and lower A1c. Subjects who used the sensor at least six days per week, which was counted as 100% adherence, saw an average decrease in A1c from 8.6% to 7.7%. Those with less than 60% adherence actually saw their baseline A1c levels increase from a mean of 9.45% to 9.63% (this was not statistically significant so not newsworthy in our view).
    - Insurers are reluctant to reimburse for CGM due to the lack of superior efficacy.
    - Physicians may be reluctant to interpret vast quantities of CGM data in light of limited consultation time available per patient.
    - In addition to STAR3, the JDRF CGM study will also be instrumental for generating reimbursement for CGM. The JDRF trial is aimed at finding the effect of RT-CGM on A1c levels, frequency of severe hypoglycemic events, and percentage of blood glucose sensor values in the range 70 mg/dL to 180 mg/dL (~4 mmol/L to 10 mmol/L).
- **We believe adherence will always be lower the less developed the technology is**, so for adherence to be a major focus of a *JAMA* piece on CGM is unfortunate. In our view, it is possible that negativity surrounding current reliability could kill the CGM market. One example: the *JAMA* piece notes that the large quantities of data generated by CGM devices make some physicians reluctant to incorporate this data into clinical practice settings where time constraints abound. Although this is true, what isn't emphasized is that trials like this are useful for clinical development *and* that companies are still working to make devices simple enough for HCPs to easily teach and patients to easily use. It's not all about how time consuming CGM will be for HCPs – it's about how patients will be able to use CGM so they can more ably manage diabetes and avoid both short- and long-term complications.
- **In writing about adherence, the article highlights that patient indifference/inaction to CGM-generated information is a major barrier** – we would certainly agree that if patients aren't motivated to improve their glycemic control or if they aren't well-educated on how to interpret information stemming from the new technology, it is less likely that they will actually see A1c improvement. That's just a good reason to start with motivated patients, given how difficult diabetes care is generally – not a reason to kill the market! (Not that *JAMA* is advocating this, but negative pieces early on in the lifecycle of a technology certainly don't help.)
- **According to the article, barriers to CGM utilization also include high costs and physician apprehension – as well as patient adherence.** We believe economic data will be generated that will show CGM is worth the cost. We also posit that the reliability will improve (this has already happened with both DexCom's SEVEN compared to the STS). The simpler the products can be, the easier it will be for HCPs to teach how to best use the devices – we look at how pumps have changed over time and have become simpler and expect that the same will happen with CGM, as long as the market can develop. To date, the lack of efficacy data and long-term studies showing that CGM reduces morbidity and mortality associated with diabetes make insurers reluctant to reimburse CGM technology – we say, walk before you run! The data are being generated now, and we hope the design of the trials will allow "real world" experiences to be reflected.

- **The article underscores that patient action on CGM-generated information is necessary for proper and effective use of CGM.** Again, we see this as an important point, though not necessarily surprising or that newsworthy. The subset analysis also showed that patients with less than 60% adherence had a baseline A1c *rise* from a mean of 9.5% to 9.6% – whereas the adherence data showing better A1c improvements among patients who use the device frequently are statistically significant, these data aren't, so we worry about too much focus on this point. As Dr. Hirsch said at ADA "These people with the higher [A1c levels] were not taking care of their diabetes before the trial, and if they're not interested and focused, this won't help them." In order to see the impact of CGM on glycemic control, Dr. Hirsch suggested enrollment of motivated patients – we agree that this is a better population to start with! Said Dr. Aaron Kowalski of the JDRF: "…there's interest in a new generation of technology that many of us in the field think [is] functional… but now we want to demonstrate through studies that it works.[1]"
- **Although we have experienced challenges with CGM using early generation devices, we believe that especially as reliability improves, CGM has potential to be of enormous help to patients**. As long as the major outcomes trials can show A1c reductions of at least 0.5% (we would expect this to happen) and less hypoglycemia, we think at least for type 1 patients, more standard reimbursement will eventually emerge. All in all, we're definitely more positive on CGM now than we were entering the summer – this reflects what we saw as a very positive reception for CGM at ADA and AADE as well as what we perceive as a greater understanding for who should use CGM. To date, what trials, real world use, and expert opinion seem to suggest is the most benefit for the following groups: 1) very motivated type 1 patients; 2) motivated patients on insulin; 3) pregnant patients; 4) patients suffering from complications like gastroparesis and hypoglycemic unawareness; 5) patients with recurrent hypoglycemia; 6) patients who have big problems with postprandial hyperglycemia; and 7) patients who need help titrating new medications (Symlin, etc). We expect the target population to expand as reliability and quality improve – but we always come back to the same point: ability to self-manage is incredibly important and thus, the educational component of any new technology is key. Currently, our healthcare system reimburses acute interventions (e.g., ER visits) much better than preventive interventions – here's to some change on that front.
- **Overall, we think it's positive that CGM is receiving more visibility, but we think this article's tone is unfortunate** because the average HCP might just look at the headline and perceive that CGM won't really go anywhere as a commercial product. We "get it" that the payers want evidence based on randomized controlled trials, but in diabetes, especially type 1, we think "real world" experience may lend more intelligence. For example, a technology trial is very different from a trial that tests a new oral agent – the former is far more nuanced: patients are working with understanding different insulin sensitivities, response rates, reactions to hypoglycemia, etc – so we are cautious in interpreting a trial like this that only examines A1c (as the *JAMA* article seems to). As we understand it, STAR1 was really more a feasibility trial – probably most useful for clinical development of technology and planning

[1] **As previously discussed, JDRF's randomized controlled trial will compare the effect of CGM on diabetes management versus conventional fingersticks.** The Randomized Study of Real-Time Continuous Glucose Monitors (RT-CGM) in the Management of Type 1 Diabetes began enrolling 450 patients at 10 sites in December 2006. Participants are randomly selected to use CGM or the fingerstick method of glucose monitoring for six months, with frequent contact from clinicians to review their diabetes management. Members of the CGM group will be monitored for an additional six months after the initial study period with less intensive contact to see if any benefits from the initial study period are sustained. The control group will use CGM with less intensive contact with clinicians. The study is aimed at finding the effect of RT-CGM on A1c levels, frequency of severe hypoglycemic events, and the percentage of blood glucose sensor values in the range 70 mg/dL to 180 mg/dL (3.9 mmol/L to 10 mmol/L).

larger trials like STAR3. We worry that people will jump to conclusions, however, on the results that focus purely on A1c.

—by Kaku Armah and Kelly L. Close

8. "Nature and causes of trends in male diabetes prevalence, undiagnosed diabetes, and the socioeconomic status health gradient"

In a paper published in the Proceedings of the National Academy of Sciences, Dr. James P. Smith of the RAND corporation investigates trends in diabetes prevalence across several socioeconomic status indicators over the past 25 years. He finds that approximately one in five male diabetes patients are undiagnosed today, a tremendous public health problem but a great improvement from 25 years ago, when approximately half of male diabetes patients were undiagnosed. Disparities in undiagnosed diabetes rates between ethnic and racial groups have largely vanished, although the differences have grown across other measures of disadvantage, such as education. Dr. Smith's didn't examine trends in women because he couldn't separate data on gestational diabetes, so the majority of his conclusions are on men.

- **The prevalence of diabetes grew considerably over the past 25 years**, from 6.0% of the overall population in 1976-1980 to 8.9% of the overall population in 1999-2002. This increase was largely due to the growing incidence of obesity, which increased from 13.1% of the overall population to 28.2% of the overall population during the same period. While obesity and other risk factors for diabetes have grown, these factors have been partially offset by improvements in the education of the population.
- **Although undiagnosed diabetes remains a significant public health problem, the rate of undiagnosed diabetes has fallen considerably over the past 25 years.** Whereas in 1976-1980 nearly half of all diabetes was undiagnosed, that number fell to 21.6% in 1999-2002, the last date in which the survey was completed. Equally encouraging, disparities in undiagnosed diabetes rates between ethnic and racial groups have largely vanished. Whereas in 1976-1980, nearly two-thirds of diabetes in Hispanics was undiagnosed, today the number is 21.4% or roughly equivalent to the 21.2% of diabetes that is undiagnosed in White, non-Hispanics. Sadly, there continues to be a higher rate of undiagnosed diabetes among the obese, a group that is at an elevated risk of developing diabetes.
- **In the past 25 years, the disparities in undiagnosed diabetes grew across other socioeconomic differences, particularly education.** Interestingly, there is no statistically significant association between education and rate of diagnosed diabetes. However, there is a strong and statistically significant relationship between education and rate of undiagnosed diabetes. Similarly, a lower income level is positively correlated with a higher prevalence of diabetes. In our interview with Dr. Smith, he suggested that this was just as likely the effect of having diabetes on income rather than the reverse. Dr. Smith underscores that, "diabetes especially in the more severe manifestations affects people's ability to earn money and lowers their future income."
- **Individuals in lower education groups are particularly at risk of developing diabetes and related complications.** As of 2002, the less educated (no high school degree) are three times as likely to develop diabetes as the general population. If they develop diabetes, they are significantly more likely to be undiagnosed and therefore to remain untreated. If diabetes is diagnosed, the less educated have more difficulty fully adhering to the current treatments

—By Nadav Klein and Mark Yarchoan

9. In The News: New IFCC, ADA, EASD, and IDF consensus guidelines

Over the past few decades, the A1c has become the most widely used measure of glycemic control. It is a measure that both clinicians and patients recognize, using it to make critical treatment decisions. Given the global importance of its use as a reference system, it is essential that the A1c assay is standardized worldwide. To make a valid standard anchor for A1c reporting, the International Federation of Clinical Chemistry and Laboratory Medicine (IFCC), in coordination with the American Diabetes Association (ADA), the European Association for the Study of Diabetes (EASD), and the International Diabetes Federation (IDF), have devised a new reference system for the A1c assay. Whereas the current A1c assay is harmonized on reference methods that measure a mixture of glycated hemoglobin, the new reference method specifically measures the concentration of only one molecular species of glycated A1c. The consensus statement reached by the above organizations in a meeting held on May 4th in Milan, Italy, states that the A1c results will be reported in IFCC units (mmol/mol) and derived NGSP units (%) using the IFCC-NGSP master equation. The IFCC has advocated the use of mmol/mol because it is scientifically correct and will therefore keep with the measurement of other analytes.

Recently there have been discussions about replacing the A1c altogether with average plasma glucose. This discussion was featured prominently at the American Diabetes Association (ADA) annual meeting in a session entitled, "Can 'Average Blood Glucose' Replace the A1C?" Nonetheless, our consensus from this meeting is that such a change is highly unlikely, particularly in the US, and if it were to occur, it would be a slow transition. While patients and clinicians have assumed that the A1c is a clear reflection of average glucose over the past few months, the data supporting this assumption are not robust.

To better understand the relationship between the A1c and average blood glucose, an international study has been initiated to study the association between capillary measurements and continuous glucose monitoring. The results of this study are due next month at EASD, but Dr. Nathan shared some preliminary trial data at ADA. If the trial is successful (and the preliminary results presented at ADA were certainly encouraging), the results will provide an algorithm allowing clinicians to convert from A1c measurements to average blood glucose, and vice versa. The IFCC, ADA, EASD, and IDF consensus guidelines state that this algorithm should be used to report an A1c derived average glucose (ADAG) value as an additional interpretation of the A1c result. Finally, the consensus guidelines require that glycemic goals appearing in clinical guidelines are expressed in IFCC units, derived NGSP units, and ADAG units.

The reporting of all three sets of units is probably a relief to many patients and clinicians who feared that a very recognized unit – the A1c – would be forever replaced. At the same time, adding ADAG units may allow patients to better conceptualize their glucose control. Whereas A1c is a relatively abstract phenomena for patients, average blood glucose is a seemingly simple construct that may be easier for patients to understand. From the preliminary "average plasma glucose study" results that were presented at ADA, it is almost certain that converting from any unit set forth in the consensus guidelines to any other unit will be a seamless process.

—By Michael X. Chen, Mark Yarchoan and Kelly Close

10. Conference Preview: 43rd EASD Annual Meeting; September 18-21, Amsterdam http://www.easd.org/

Longtime readers won't be surprised that we're very excited about the European Association for the Study of Diabetes (EASD) annual meeting, which this year is being held in Amsterdam. This

is traditionally one of the very best diabetes conferences of the year – lots of data, lots of new products, and lots of cocktails. And autumn in Europe? What could be better! Last year, the big ticket EASD item was the release of the DREAM trial results. As we prepare for this year's meeting, here are the oral sessions and poster presentations to which we're most looking forward.

Tuesday, September 18

EASD will open with a lecture from A. Hattersley entitled, "*From base change to better care: the clinical impact of molecular genetics*." In the afternoon, there is a symposium about whether mean blood glucose will substitute for A1c. The symposium is chaired by Dr. David Nathan, who as noted above, discussed the preliminary results from a study at ADA about whether it is possible to convert effectively from A1c to mean blood glucose and vice versa. We expect Dr. Nathan to present positive data from this study.. We will also be attending a symposium about the special biology of visceral fat tissue, and a combined EASD/JDRF symposium about beta cell imaging and regeneration.

Numerous fascinating EASD abstracts will be presented in poster sessions rather than oral presentations. Poster event A will include a session about *incretin effects* (PS 43), as well as a most likely sobering review of the *socio-economic aspects of diabetes* (PS 103). In poster event B, we are especially looking forward to attending PS 86 on *novel therapies and drugs*, which will have a highly-awaited session on amylin and type 2 patients (#913) – the rest of this session will be interesting to watch.

Wednesday, September 19

Wednesday will open with an intriguing set of debates held in Rembrant Hall. Dr. Alain Baron (United States) will debate Dr. Edward Gale (United Kingdom) about *whether we are getting value for our money out of drugs for diabetes*, with Dr. Baron arguing yes and Dr. Gale arguing no. In the same symposium, there will be a debate about *whether GLP-1 based therapies will replace sulfonylureas*, with Dr. J. Holst (Denmark) arguing yes and Dr. Matthews (United Kingdom) arguing no. Our impression is that clinicians are indeed using incretins to replace sulfonylureas, though of course they don't yet have nearly the decades-long safety record of the SU class. Dr. Holst is always an excellent speaker and we look forward to hearing him address the pros and cons of GLP-1 treatments.

Later in the day will be oral presentations on *thiazolidinediones* (OP 13), which we're looking forward to, though we don't expect to see any new data that will truly clarify the hanging question of Avandia and CV risk. Oral 0074 is a comparison of C-reactive protein reductions with rosiglitazone (Avandia), glyburide, and metformin, while 0078 is about a possible association between rosiglitazone and reduced bone formation at earlier stages in postmenopausal diabetic women – this may shed light on the mechanism connecting TZDs to fractures. Given all of the recent controversy involving TZDs, these presentations will most likely be extremely popular. Perhaps even more interesting are a number of presentations about *GLP-1 based therapies* (OP 19). This includes 0111, which describes the complementary effects of DPP-4 inhibitors and metformin. Also worth looking at are a number of poster presentations about diabetes and cardiovascular disease, including 0097 and 0098, which are about the association between good glycemic control and cardiovascular outcomes; and 0099, which is about the relationship between cardiovascular disease risk and the use of insulin from a large national observational study.

Within poster event C, poster sessions PS 57, about *DPP-4 inhibitors*, and PS 81, about *metformin and sulfonylureas*, are very clinical and will surely draw a big crowd. In poster event D, we're excited about PS 76, which will give us an *update on anti-obesity drugs*, including rimonabant, which of course has been approved in Europe but not in the US.

Thursday, September 20

In the morning, we are looking forward to the EASD/ISPAD symposium about *therapeutic challenges for children*. Within this symposium, we are most excited about hearing Dr. Danne (Germany) speak about real-time glucose sensing and pumps in children with diabetes. Dr. Hanas (Sweden) will give an overview of treatment options for very young children. Of course the biggest event on Thursday is the *42nd Minkowski Lecture*, which this year will be given by Rockefeller star Marcus Stoffel.

Two Thursday oral presentations of particular interest are OP 7, which is about *body weight regulation*, and OP 8, which will discuss the *physiology and pharmacokinetics of insulin therapy*. We look forward to the head-to-head comparison of the effects of long-acting insulin analogs glargine (Lantus) and detemir (Levemir) on glucose and lipid metabolism in T1DM that will be presented in OP 8. We will also stop by OP 12 to learn about the *prevalence of childhood diabetes and mortality in type 2 diabetes*, which we understand is increasing a faster rate than type 2, with particularly devastating consequences in terms of early complications.

Poster session E will include PS83 – the last of two poster sessions about *DPP-4 inhibitors*. In poster session F, poster presentation PS78 will cover a number of studies about *liraglutide* – we would be extremely interested to see a poster on the results of the LEAD 5 study, which have not yet been published or presented. PS 95 will discuss *insulin analogs in type 2 diabetes*.

Friday, September 21

On the last day of EASD, Dr. Snoek from the Netherlands will give a lecture about *treatment adherence in type 2 diabetes*, and there will be a morning symposium about the Treating To Target in Type 2 diabetes (4-T) study on insulin therapy in type 2 diabetes – this may well be the most fascinating sessions at EASD, as initial basal insulin therapy goes head to head against mealtime insulin

A number of exciting oral presentations have been reserved for this last day as well, including OP 37 about *novel therapies* – one that we'll look forward to is IN-105, an oral insulin While we're constantly looking for new tools, oral presentation OP 38 will review ways of optimizing treatment with the oldest but still most valuable tool we have – *insulin*. This session starts with a meta-analysis on pump therapy vs MDI – we're holding our breath. Also being discussed will be intraperitoneal insulin delivery, through this different kind of pumping. OP 43 will review recent *clinical trials with metformin and sulfonylureas*. We are not as excited about this as we are curious to gauge MD interest. At the conference closing, new EASD honorary members will be inducted, and E. van Obberghen will give the *39th Claude Bernard Lecture*.

—by Mark Yarchoan and Kelly Close

11. Conference Preview: 2nd Annual Cardiometabolic Health Congress; September 27-29, Boston, MA http://www.cardiometabolichealth.org/

We're looking forward to this year's CHC meeting, where we hope to meet world-renowned experts, be introduced to some cutting-edge science, and learn medical and surgical approaches to manage obesity, diabetes and cardiovascular disease. As a one-track conference, it shouldn't be too hard to take in everything, but here are a few sessions that you should definitely not miss!

Wednesday, September 26

Though the conference has yet to start, we are already looking forward to Dr. William Cefalu and Dr. John Gerich discussing "*Prandial Insulin and Cardiovascular Risk.*" With more aggressive

insulin-centered treatments being introduced for type 2 diabetes, we think that it will be very interesting to hear what these two speakers have to say on its impact on CVD risk.

Thursday, September 27

Thursday's keynote speaker is Dr. Ronald Kahn, who will be present "*The Science Behind Insulin Resistance and Its Impact on Cardiometabolic Risk*" at 8:15-8:45 am. We feel that though this subject is a cornerstone of diabetes, it has not been fully explored and we look forward to seeing Dr. Kahn report his findings.

Following him, Dr. Martin Abrahamson will present "*Pharmacotherapy for the Management of Type 2 Diabetes*" from 8:45-9:15 am. We will be interested to see the extent to which there will be some mention of new therapy options and how to incorporate them into clinical practice in his presentation.

From 10:45-11:15 am, Dr. Bernard Zinman will host "*Type 2 Diabetes: Interdicting Disease Progression.*" We eagerly await his suggestions and his talk – we learn a huge amount listening to him time and again.

Dr. Jay Skyler will moderate the first panel discussion with Dr. Hertzel Gerstein, Dr. Richard Kahn, Dr. Larry Leiter, and Dr. Richard Nesto at "*Diabetes Prevention: Does it Work? Is it Worthwhile?*" from 11:45-12:30 pm. With pre-diabetes on the rise and obesity rates hitting record highs, this certainly promises to be an interesting talk, particularly now that the TZDs have been discredited as a tool for preventing diabetes.

During the lunch symposium, Dr. Paresh Dandonna, Dr. Jack Leahy, and Dr. Richard Nesto will present "*Cardiometabolic Risk Management: The Role of Insulin Therapy in Achieving Glycemic Control.*" We hope that this will complement Dr. Cefalu and Dr. Gerich's talk on Wednesday, and it will be interesting whether these two presentations agree on the role of insulin therapy.

From 2:30-3:00 pm, Dr. Kitt Petersen will present "*Is It Visceral or Ectopic Fat Deposition, or Is It Both?*" This should help expand some of our understanding of the different fats and their impact on diabetes risk and implications. As a reminder, visceral fat is located inside the abdominal cavity and is metabolically more harmful than subcutaneous fat, which is located under the skin. Ectopic fat describes fat that has been deposited where it doesn't belong, such as in the liver or in skeletal muscle. While to two types of fat often overlap, they don't always describe the same thing.

Later on, from 4:00-4:30 pm, Dr. Louis Aronne will discuss "*Pharmacotherapy for Obesity Management: Current Practice and Future Directions.*" Following the FDA's recent rejection of rimonabant and the commercial success of Alli so far, this talk may provide some insights on future drug treatments for obesity.

Immediately following, Dr. Matthew Hutter will host "*Bariatric Surgery: Patient Selection, Procedure Options, and Outcomes"* until 5:00 pm. Bariatric surgery is certainly on the rise as it is currently the only potential cure for patients with type 2 diabetes, and it should be interesting to see what Dr. Hutter's view is.

Closing the Thursday sessions, during the evening's dinner symposium, Dr. Henry Ginsberg, Dr. Michael Schwartz, and Dr. Steven Smith will talk on "*Emerging Concepts in Obesity Management: Integrated Neurohormonal Therapy.*" This novel topic, first piloted by Amylin, is certain to draw a large crowd and is a must see for anyone interested in the intersection between diabetes and obesity treatment. Be sure to get your reservations early!

Friday, September 28

From 9:15-9:45 am, Dr. Christie Ballantyne will present "*Biomarkers and Noninvasive Imaging: Useful, Hopeful, or Hype?"* We expect that he will discuss some of the biomarkers currently being studied as potential predictors of cardiovascular disease, such as CRP and other compounds associated with inflammation. While there is a growing research base linking cardiovascular disease to chronic low-grade inflammation, our impression is that most of the new markers don't add too much additional predictive value on top of the easiest and cheapest ones already used in risk calculators like the Framingham risk score or the diagnostic criteria for metabolic syndrome, like age, family history, BMI, etc. If these markers could be measured non-invasively, however, they could be a cost-effective way to improve risk predictions.

Dr. Peter Wilson will be discussing "*Risk Assessment Models to Predict Multiple Cardiometabolic Risk Factors"* from 10:15-10:45 am. As we're sure everyone is aware by now, patients with diabetes have significantly higher CVD risk, and we would like to see what additional insights Dr. Wilson's models may provide.

One Friday lunch symposium will focus on Dr. Louis Aronne, Dr. Deepak Bhatt, and Dr. Robert Eckel's work on "*The Role of the Endocannabinoid System in the Management of Cardiometabolic Risk.*" This seems to be a repetition from previous years, and we're really curious to see what's new for this presentation.

Later in the afternoon, Dr. Sonia Caprio will talk on "*Glycemic Control in Children with Type 1 or Type 2 Diabetes*." Diabetes in children, both type 1 and type 2, is emerging as a major public health threat, and as we heard Dr. Neil White point out at AADE, there is currently no consensus on what to do for type 2 pediatric patients after metformin.

Saturday, September 29

From 8:15-8:45 am, Dr. Allen Spiegel will present "*The Impact of Personalized Medicine on the Management of the Obese Patient with Multiple Cardiometabolic Risk Factors*." Dr. Spiegel has recently stepped down from his post at the NIH and should be able to provide a unique perspective on the trends toward more personalized medicine.

Following his talk, Dr. Robert Toto will discuss "*Early Kidney Disease: The Underappreciated Cardiometabolic Risk Factor*" from 8:45-9:30 am. The key word here is, of course, "underappreciated," as kidney disease is certainly an important and unfortunate consequence of diabetes. It should be interesting to see if Dr. Toto has any new research on this topic.

Right before lunch, from 11:00-noon, Dr. Richard Nesto will moderate Dr. Christie Ballantyne, Dr. Robert Eckel, and Dr. Steven Haffner on "*ACC, ADA, AHA, EASD and ESC Highlights: Latest Data and Implications for Clinical Practice.*" This is a really important talk and a must-attend for everyone interested in the new data that have been showcased over the past year. If nothing else, it will certainly bring the audience up to speed on the newest aspects of diabetes care.

—by Michael X. Chen, Jenny Jin, Mark Yarchoan and Kelly L. Close

12. Diabetes Revenue Watch, Diabetes Market Index, and Random Thoughts:

We were playing around with some numbers yesterday and put the charts together below. The Close Concerns Revenue Watch will track revenue growth for major companies and franchises in the sector, while the Close Concerns Diabetes Market Index will track stock prices of major diabetes "pure plays" (or close "pure plays" like Novo Nordisk) over time. Looks like Novo Nordisk's stock is the big winner on the stock movement front in terms of year-to-date

performance, up 54%. On the revenue front, Amylin, Medtronic, and Sanofi have all had striking increases in the second quarter.

Close Concerns Diabetes Revenue Watch

	2Q07 Revenue	YTD Revenue	2Q06 Revenue	1H06 Revenue	ΔQ	Δ1H
Abbott - Diabetes Care	USD308	USD593	USD290	USD563	6%	5%
Amylin - Total Revenue	USD197	USD369	USD118	USD200	67%	84%
Bayer - Diabetes Care	EUR244	EUR470	EUR213	EUR406	15%	16%
Dexcom - Total Revenue	USD863	USD1,875	USD479	USD494	80%	280%
Eli Lilly - Humalog/Humulin	USD601	USD1,167	USD540	USD1,063	11%	10%
GlaxoSmithKline – Avandia	USD692	USD1,503	USD870	USD1,542	-20%	-3%
Johnson & Johnson – LifeScan	USD596	USD1,145	USD522	USD1,027	14%	11%
Medtronic - Diabetes Care	USD241	USD470	USD196	USD384	23%	22%
Merck – Janumet	USD24	USD24	USD 0	USD 0	N/A	N/A
Merck – Januvia	USD144	USD231	USD 0	USD 0	N/A	N/A
Novo Nordisk – Diabetes Care	DKK7,652	DKK14,795	DKK6,868	DKK13,372	11%	11%
Roche - Diabetes Care	CHF789	CHF1,544	CHF746	CHF1,428	6%	8%
Sanofi-Aventis – Lantus	EUR503	EUR961	EUR421	EUR803	19%	20%
Takeda – Actos	JPY Bil.107	JPY Bil.189	JPY Bil.84	JPY Bil.151	27%	26%

*All figures in millions unless otherwise indicated

Close Concerns Diabetes Market Index

	23-Aug-07	29-Jun-07	30-Mar-07	3-Jan-07	30-Jun-06	ΔQ[1]	ΔYTD[2]	ΔYR[3]
AMLN	50.07	41.16	37.36	36.32	49.37	10%	38%	(17%)
BIOD	17.66	19.80	-	-	-	N/A	2%	N/A
DXCM	8.9	8.19	7.86	9.88	13.58	4%	(10%)	(40%)
GSK	51.58	52.37	55.26	53.81	55.8	(5%)	(4%)	(6%)
HDIX	9.43	11.77	10.82	10.61	-	9%	(11%)	N/A
MNKD	8.87	12.33	14.30	16.16	21.31	(14%)	(45%)	(42%)
NVO	109.95	108.57	90.53	83.46	63.59	20%	32%	71%
OREX	13.9	15.02	-	-	-	N/A	7%	N/A
PODD	17.06	14.20	-	-	-	N/A	7%	N/A
SIRT	13.94	9.87	-	-	-	N/A	30%	N/A

[1]End of 2Q07 compared to end of 1Q07
[2]Beginning of FY 2007 compared to 24-Aug-07
[3]End of 2Q07 compared to end of 2Q06

Random Thoughts: So at Close Concerns we all try to talk a lot about what we're doing short-term, long-term, what we did today (until a publication or press release took us by surprise), what our plans are, etc. We write these messages every day and it's a pretty remarkable way to stay on the same page as everyone else here. Our summer associate Mike Chen started something last winter (he worked for us then too – we are so incredibly sorry he's leaving to go back to Amherst

soon that we can't even think straight) where at the end of his daily updates, he would write "Random thought" and truly, although they are quite random, they are often quite the best part of the day. So here's to random thoughts – and the ones for this issue: :

If you are in San Francisco, you must go see Hiroshi Sugimoto's exhibit at the De Young Museum, on 'til September 23. "Time, memories, dreams, natural histories" as the San Francisco Sentinal said it – don't miss it, you'll be so glad you didn't! It's the best museum exhibit I've been to in a decade and I have been to about five thousand.

Mike's random thought of the day today, by the way, was "Either control your attitude or you will be offered medication." We're not sure where that was directed …we asked him where this came from and he said he found it "in some research he did for Close Concerns."

--Kelly L. Close

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