Diabetes Close Up, V3, #15
December 31, 2004
Year-End Diabetes Goings-On

Happy New Year!
T h e s h o r t e r v e r s i o n

We're just getting ready to ring in the new year in San Francisco – by the time you see this, most of you, we suspect, have already celebrated! We hope celebrations were safe and happy. Our year-end ten-part newsletter features a few recent news items in the world of diabetes; discusses recent meetings and tail-end third quarter earnings calls of note; and previews important meetings in early 2005. Read on for more news on …

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   - Part 3: Diabetes Technology Society, Philadelphia, PA – October 30-31, 2004
   - Part 4: 3Q04 earnings reports – Novo Nordisk, Sanofi-Aventis, Merck, B-D, Alkermes, Nektar, Polymedica
9. **Key Early 2005 Conferences –** JP Morgan, ADA Postgrad, 1st International Congress on Prediabetes and the Metabolic Syndrome, and the Clinical Diabetes Technology Meeting (the last two are brand new meetings with stellar speakers/lineups – we're very impressed~)
10. **From Close Concerns and *Diabetes Close Up* –** we thank you so much for your support in 2004 and wish you all a happy, healthy, and successful new year.

The longer version

1. **J&J – Doing Some Early Christmas Shopping by Buying Guidant and Signing An Agreement With Arena:** Johnson & Johnson has been busier than ever of late. In addition to purchasing Guidant (as you know, a leader in coronary stents and cardiac rhythm management) in mid-December, JNJ's Ortho-McNeil division announced an agreement with Arena Pharmaceuticals on December 21 for the development of two pre-clinical diabetes compounds.
   - The compounds covered by the agreement concern the 19AJ receptor (an orphan G protein-coupled receptor – GPCR's are a hot area of research at the moment) and theoretically offer the possibility of a glucose-sensitive secretagogue. While precise details were not released, Arena claims that the deal could ultimately be worth up to $300 million, with $17.5 million of that up-front. Recall that although J&J paid $24 billion for Guidant, J&J had over $7 billion in cash on its balance sheet at the end of last quarter and always has room for additional strategic purchases.
   - Although there's never any information ahead of time, we doubt J&J will be on the sidelines on the diabetes/obesity M&A front for long, having announced the Inverness deal now nearly four years ago (May 2001). We don't anticipate the Guidant purchase will create distractions at LifeScan, given that the operating companies are managed separately (at last count, there were a whopping 200-plus). We view the acquisition as a positive for J&J from the perspective that it further strengthens potential metabolic disease synergies, and may ultimately manifest in increased competitiveness for J&J's diabetes (LifeScan, pharma), obesity (Obtech, pharma), and cardiovascular businesses (Cordis), across the board.
2. **Bristol Myers-Squibb – Muraglitazar Is with the FDA Now:** On December 23, Bristol Myers-Squibb (partnering with Merck) announced that it had filed an NDA for muraglitazar, its dual PPAR-agonist compound. The company had said for some time that it would file by the end of the year, so this isn't surprising news, though many wondered with just six business days left 'til year-end. As always – but *more* so now, in the Vioxx-should-we-say-Celebrex-should-we-say-Aleve era - it is difficult to predict the potential course of the FDA. Although Bristol maintains that all of the necessary safety data is in place for muraglitazar, recent FDA concerns about dual PPAR-agonists' safety have thrown several other companies' regulatory timelines into disarray. Given the cloud over all dual PPAR-agonists in general, and the fact that muraglitazar is the first of its kind to go before the FDA, we expect rather pointed questions at its panel meeting (we assume a panel is a certainty, not a question). As such, we don't expect to see approval until late 2005 at earliest.
   - As a quick reminder, PPAR (peroxisome proliferator-activated receptor)-agonists target intracellular receptors that regulate glucose and lipid homeostasis within the body. PPAR-gamma agonists (for instance, Lilly's pioglitazone) help re-sensitize the body to insulin. Dual PPAR-agonist drugs have looked especially promising as they may offer the hope of effectively lowering glucose without the troublesome weight gains associated with virtually all medications (sans Metformin, which has other GI problems in some patients) currently on the market. That said, we still wonder exactly *what* is being inhibited in compounds in this class – still a major question.
   - Potential players in dual PPAR-agonists include Aventis (AVE-0847), Glaxo (677954), and J&J (MC-555, or Isaglitazone), among others. We believe all these compounds are in phase 2 but won't progress to Phase 3 anytime soon since all are back to rodent studies, per the FDA actions last summer (see DCU #11 for more information. If you are interested in our detailed database in which pipeline drugs for all public companies are reviewed, please write us at info@closeconcerns.com).
3. **Takeda Shelves TAK-559.** On Dec. 22, Takeda Pharmaceuticals announced that it was shelving its Phase 3 drug known as TAK-559 because of some liver enzyme abnormalities in a small group of study patients. Expectations for this drug were as high as $3 billion a year. Although the company is publicly keeping a stiff upper lip, emphasizing that the program is on hold pending further research,

we would be surprised if this drug re-enters trials again. Takeda does have a "back up" in the form of TAK-654, currently in Phase 2 studies. Given the upcoming Actos exclusivity expiration (likely 2006, although depending on extensions, this could change, and as always, official expiration varies according to whom one asks), Takeda is clearly concerned about maintaining the strength of its diabetes franchise, to which Actos has been a powerhouse addition.

4. **Animas Buys Cygnus Intellectual Property.** Animas announced on Dec. 17 an agreement to acquire essentially all of Cygnus's assets and rights for $10 million in cash. Thus ends a long and ultimately disappointing story for those who have followed Cygnus as a public company. In our view, Cygnus always had valuable technology – the fact that it did not ultimately realize its goals may translate into real upside for Animas.
    - At a meeting last year on continuous monitoring sponsored by UCSD, former Cygnus VP of R&D (and noted diabetes research expert) Russ Potts gave a prescient talk on continuous monitoring, emphasizing that technology was necessary but not sufficient, and that numerous barriers needed to be overcome for continuous monitoring. He offered detailed insights on issues related to user acceptance, healthcare provider acceptance, regulatory approval, and reimbursement – one of the best talks we heard all year. We don't believe there is any doubt that Cygnus's intellectual property (particularly glucose sensing technology) is valuable and we believe Animas can leverage relevant patents successfully.
5. **MannKind Takes Another Small Step for Itself.** MannKind announced on December 22 Phase 2b results from a clinical study of its Technosphere Insulin (an inhaled insulin formulation). One-hundred-twenty-three patients were enrolled at 21 sites and the company notes that a "highly statistically significant" number achieved the trial's goal of an HbA1C reduction of 0.6%. Side effects, where noted, appeared to be tolerable and only 13% of the total patients dropped out before the end of the study. While a great deal of information was not released (we look forward to learning more upon publication of results or at the 2005 ADA), we believe the results were basically positive. That said, this compound is a latecomer and as yet does not have a larger development partner – though we suspect that is not for long and some very interesting partnership negotiations are likely being orchestrated by the master negotiator himself, Al Mann. We look forward to learning more, specially more details on dosing, what other drugs, (if any), the groups participants were taking going into the trials, sub-group outcomes, and side effects, outcomes, e.g., safety and weight, etc.). With Phase 3 trials likely to start next year, 2005 could be very interesting for MannKind.
6. **Conjuchem Shows More Data, Sort of:** On December 15, Conjuchem offered more data on its phase 1 study for a reformulated DAC GLP-1 monotherapy, terming the preliminary results for DAC:GLP-1 "materially positive." We interpret this characterization cautiously. For us, it seems reasonable that tolerability was improved and that the diluent saw solid progress. In terms of timing, we don't imagine the company could file before 2007, bringing this to market 2008 at the earliest. We don't look for this compound to be competitive against Amylin's LAR.
    - On the phase 2 study, Conjuchem gave very parsed data. Results were tough to interpret because the company did not give much info on outcomes of the lower dose of DAC, nor were they clear which sub-groups were being discussed. Additionally, they were not clear on various items like A1C change from of baseline (vs. placebo), the bane of our existence. Conjuchem discussed only to the high-dose cohort, the low-dose cohort data may not be that promising - although the company described the drug as "*highly effective ... even at low dose levels, and tolerable - re-establishing this compound's potential to become a best-in-class product*." We were surprised, at this stage, given the size and stage of the study, to see the drug characterized this way. Our take on the data:
        - **A 1.01% HbA1C reduction** seems decent, but not fantastic, assuming at least part of that gain reflects a placebo group's increase in A1C. In other words, it may be competitive early on but not compelling longer-term – again, tough to say, because we don't know the whole story (not just on baseline vs placebo results, but also on side effects, etc.)

- **Speaking of side effects, weight loss of 5.6 lbs** is difficult to assess given the short period of the study and the high nausea rate. This is about 2.8% of total average body weight.
- **The drop-out rate overall was still high at 27%.** For the DAC groups, we see 20% dropout for the the high-dose group as high, and 28.5% for the low-dose group is obviously also quite high - though neither of these rates was as high as had been seen earlier (over 50%). We raise our collective eyebrows at the disclosure that 5% of the 85 participants had serious protocol violations. How hard is this drug to use, we wonder? We will stay tuned for more info
- **Data to look for at ADA** – more information on 1) baseline vs. placebo groups; 2) sub-groups analyzed (ITT, completer, etc.); 3) dosing; 4) drop-outs.

7. **Plexxikon and Wyeth Collaboration** – On Oct. 29th, Plexxikon and Wyeth Pharmaceuticals announced a collaboration to develop treatments for type 2 diabetes and metabolic disorders. This represents a foray into the diabetes market for Wyeth. The collaboration is focused on the development of Plexxikon's clinical lead, PLX204, a treatment for type 2 diabetes and related cardiovascular complications, as well as several other small molecule drugs targeting the peroxisome proliferator-activated receptor (PPAR) family of nuclear receptors. Plexxikon's PPAR program is focused on discovering and developing modulators that demonstrate improved safety as well as additional therapeutic benefits compared to currently marketed therapies. PLX204 is expected to regulate levels of glucose, triglycerides, free fatty acids, HDL and energy expenditure, in a once-daily pill. Current treatment regimens require several drugs be taken in order to manage the various metabolic imbalances seen in patients with diabetes. Plexxikon will receive payments of $22 million, including an upfront license fee and multi-year research funding. Additionally, Plexxikon may earn milestone payments totaling nearly $350 million depending on the success of potential products emerging from the commercialization of products developed from the collaboration. Plexxikon also will receive royalties on future product sales and Wyeth will loan Plexxikon money to fund the company's share of clinical development expenses.

News synthesis by Stephen D. Simpson, Melissa P. Ford, Jennifer Hull, and Kelly L. Close

8. **Recent conferences, meetings, and calls of note!** See below for detailed reviews.
   - Part 1: NIH meeting: "The Role of Insulin in the Critically Ill Patient: Basic and Clinical Evidence" – Bethesda, MD, December 9, 2004
   - Part 2: Diabetes Technology Society, Philadelphia, PA – October 30-31, 2004
   - Part 3: Lilly Analyst Meeting – December 12, 2004
   - Part 4: Bristol-Myers Squibb R&D Review – November 17, 2004
   - Part 5: 3Q04 earnings reports – Novo Nordisk, Sanofi-Aventis, Merck, BD, Alkermes, Nektar, Polymedica
9. **Conferences of note to watch for**:
   - **JP Morgan 23rd Annual Healthcare Conference, San Francisco – January 13-16**
   - **ADA Postgrad, New York City – February 4-5 (www.diabetes.org/pg05):** Selected outstanding speakers include Dr. Steve Edelman on new insulins, Dr. David Cummings on bariatric surgery, Dr. Daniel Drucker of glucagon.com fame on incretins, and Dr. Anthony Furnary of Portland Protocol fame in ICU management. Powerhouse lineup right there! Other interesting sessions include the role of adipokines and inflammatory factors in metabolic syndrome and pharma for kids with type 2.
   - **1st International Congress on Pre-diabetes and the Metabolic Syndrome, April 13-16 – Berlin** (www.kenes.com/prediabetes/index.asp)**:** Check it out – obviously a huge amount of interest in this area. As readers know, we are following drug trials closely to see what drugs may receive expanded indications to slow or prevent diabetes – if we think 18 million estimated PWD is big, how about 40 million with pre-diabetes? Six, count 'em, six Big Pharma players - Sanofi-Aventis, Novartis, BMS, Bayer, Merck, and Takeda - are sponsoring symposia at this meeting.
     - We expect incredible sessions led by Dr. G. Alberti (History of Prediabetes), Dr. P. Zimmet (Prediabetes – A Global Snapshot), Dr. Ralph DeFronzo (Insulin Resistance

and Impaired Beta Cell Function in Individuals with IGT), Dr. L. Ryden (CVD and Diabetes – a Fatal Association), Dr. C. Bouchard (Genetics of Obesity), Dr. Fran Kaufman (Societal Approach to Diabetes Prevention in the Young), Dr. Sonia Caprio (PreDiabetes and Metabolic Syndrome in Childhood and Adolescent Obesity), Dr. Rury Holman (Lifestyle Diabetes Prevention), Dr. M. Nauck (GLP-1), Dr. Harold Lebovitz (Mixed PPAR-agonists), Dr. U. Pagotto (Endocannabinoids), Dr. R. Heine and Dr. R. Nesto (CVD in Pre-diabetes and CVD Risk in Metabolic Syndrome), Dr. K. Malmberg (DIGAMI).

- And there will be debates! Dr. Steve Haffner and Dr. J. Tuomilehto will debate whether there is a major difference between pre-diabetes and metabolic syndrome, Dr. Richard Kahn and Sir George Alberti will have a "transatlantic" debate on pre-diabetes versus IGT. We will hear about the epidemiology of pre-diabetes and the Metabolic Syndrome globally, with specific emphasis on Asia, India, and Africa.
- Potentially of *most* interest, key trial data from the DPP, ACT NOW, TRIOD, DREAM, NAVIGATOR, IDPP, STOP-NIDDM, ORIGIN, and DREAM will be reviewed.

- **Clinical Diabetes Technology Meeting, April 15-16 – San Francisco:** This new meeting will focus on continuous monitoring and insulin delivery (www.clinicaldiabetestechnology.org). The stellar speaker line-up will include – among others – Dr. Bruce Bode (Atlanta Diabetes Associates), Dr. Bruce Buckingham (Stanford), Dr. William Clarke (University of Virginia), Dr. Steve Edelman (UCSD), Dr. Satish Garg (Barbara Davis Center, Denver), Dr. Irl Hirsch (University of Washington), Dr. Jeffrey Joseph (Thomas Jefferson University), Dr. David Klonoff (Mills Peninsula), Dr. Darrell Wilson (Stanford), and Dr. Howard Wolpert (Joslin). The conference website will soon be updated with the full conference schedule and paper topics.

– Conference and earnings updates by Melissa P. Ford, Jennifer Hull, Olayinka A. Olowoyeye, Stephen D. Simpson and Kelly L. Close

10. **Thank you to all for your continued support** for *Diabetes Close Up*. Look for the next issue in January, 2005 when we report on the JP Morgan conference taking place here in San Francisco mid-month as well as noteworthy early earnings calls.

The super-long version

Part 1: Lilly Analyst Meeting – December 12, 2004
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Part 1: Lilly Analyst Meeting – December 12, 2004

I. Overview: Sidney Taurel, Chairman, President and CEO

1. The political climate may be better for pharma because Bush has been re-elected.
   a. Policy steps are leading towards a more consumer-driven system – free trade and IP will be respected
2. The election does not change the fact that this is one of the harshest economic climates ever
3. Taurel emphasized access for the uninsured needs to be a priority – he cited Lilly Answers and Lilly Cares programs as examples of how Lilly is making drugs cheaper or free to people on limited incomes. This will be interesting to watch, as there are skeptics aplenty on this front.
4. Recent events (read: Vioxx) mean that the future may bring more intense post-marketing monitoring.
5. Lilly has no major patent expirations for the rest of this decade – the company is trying to make up for declining US Zyprexa sales ($2.8 billion in 2003) by investing in new drugs and increasing productivity
6. Eight new products launched in 2004; seven new indications for existing and new products
   a. Cymbalta's indications have expanded – the latest one is diabetic neuropathy, a very under-treated area. We will watch how this drug does for the indication.
   b. Lilly is on the verge of expanding its diabetes profile
      i. With partner Amylin, Lilly expects to launch in 2005. Clearly, there is much excitement surrounding this launch.
      ii. Ruboxistaurin launch expected second half of 2005 – we believe the first indication will be neuropathy, followed by retinopathy, followed potentially by nephropathy. We believe the focus on reducing complications – both microvascular and macrovascular – will continue and any drugs addressing any of these well should benefit handsomely.
   c. Inhaled insulin has being moved into phase 3 trials, as the company announced in the fall.
   d. Lilly will implement a Six Sigma program in 2005. Goals are not only to reduce operating expenses growth but also to support current products and pipeline more effectively.

II. Marketed Products: John Lechleiter, Ph.D., Executive VP, Pharmaceutical Operations

1. Product portfolio has doubled since Nov. 2001
2. Three big launches coming up, including Exenatide
3. Lilly is streamlining, seeing product synergies as beneficial
4. Designing education to answer key questions from patients and physicians, etc.
5. Cymbalta
   a. Cymbalta is being reviewed for diabetic neuropathy indication in Europe
      i. Already indicated in US
      ii. 1-3M US DM pts have neuropathy
         (1) 10% of Cymbalta scripts are for neuropathy now
      iii. Right now Lilly is selling Cymbalta as an anti-depressive to PCPs and a neuropathy drug to endos, but in the next few years they'll take the neuropathy message to PCPs.

6. Lilly and Amylin are gearing up for the launch of Exenatide: Lilly is continuing to support Humalog; also moving forward with Ruboxistaurin and inhaled insulin. Notably, long-acting insulin was not mentioned. Although we saw a poster at EASD in Munich in September on a long-acting compound from Lilly, we believe this particular compound was not found to be competitive against Lantus.

III. The Lilly Pipeline: Steve Paul, M.D., Executive VP, Science and Technology

1. Lilly is closing its North Carolina plant and moving its lead generation operations to Indianapolis
2. Exenatide, analog of GLP-1; an incretin mimetic
    a. Patients and physicians know what uncontrolled diabetes can do
    b. Diagnostics (A1C tests and home blood glucose testing) help us know whether control is being achieved, yet many patients fail to meet targets on current regimens. Personally, we believe until there is a statin for diabetes, i.e., a real blockbuster, targets will remain largely unmet – on the other hand, we believe this drug will quality as a blockbuster despite naysayers who remain concerned about application, i.e., injection. We think if it really works, a lot of patients will get over this barrier. What is more necessary is for healthcare providers to get over the barrier – particularly since the drug doesn't appear to prompt hypoglycemia and is associated with weight loss, we remain very positive. In particular, we believe hypoglycemia remains a major barrier, which is such a shame, given the poor glycemic control seen in all patients – but type 2 patients in particular.
3. Ultimately, we believe that Exenatide, when approved, will create a new space in the continuum of care for patients with type 2 diabetes. As such, positioning of Exenatide: *between* oral medications and insulin – use before going onto insulin – could be powerful. And who knows eventually how early type 2 patients might take the drug, but clearly there will be more interest from healthcare providers and patients on treating diabetes earlier in disease progression. Seven million US type 2s are on oral medications alone; 3-4 years of therapy and their control deteriorates.
4. As a reminder, Exenatide:
    a. Stimulates insulin secretion only in presence of hyperglycemia, resulting in less hypoglycemia
    b. Restores first-phase insulin response, one of the earliest defects in T2
    c. Inhibits secretion of glucagon only in presence of hyperglycemia
    d. Appears to offer weight control benefits
    e. Twice-daily fixed dose injection, no need to titrate. Having seen the success in simple instructions for Lantus, we believe that the absence of need to titrate will be viewed as a *major* benefit by healthcare providers – and a plus from a patient perspective as well.
5. April 30, 2005: target date for FDA action on Exenatide
6. Lilly is partnering with Alkermes and Amylin on Exenatide LAR (long-acting release)
    a. Phase 2 multidose study of Exenatide LAR for 1x/week treatment of type 2 will begin in 1Q2005
7. Ruboxistaurin update:
    a. Inhibits diabetes-induced over-activation of PKC-beta
    b. In vision disorders, including diabetic retinopathy and macular degeneration, Ruboxistaurin increased visual acuity by about 30% compared to placebo
    c. In combination with ACE-inhibitors and ARBs, Ruboxistaurin appears to show benefits for neuropathy too
        i. This data will be presented in 2005.
    d. No significant differences apparently between the 32 mg and 64 mg doses, which we found surprising, though slide interpretation was difficult as units weren't shown.
    e. No significant side effects compared to placebo
    f. Lilly looks to file Ruboxistaurin in the US in the second half of 2005; European filing will follow
8. Actos update: Lilly hopes to demonstrate that its PPAR-agonist (Actos) raises HDL cholesterol
    a. Phase 2 studies for this will begin in mid-2005
9. Inhaled insulin update: Lilly and Alkermes are working on an inhaled insulin device that is smaller than that of competitors.

a. Using a low-density formulation that will allow more absorption
b. Phase 2 data on inhaled vs. injections in type 1s will be presented at ADA 2005

10. Obesity update: management noted that endocrine and neuroscience are coming together – working more on obesity is a common theme these days in Big Pharma and we will be interested to see where this goes at Lilly as it is early days still. Two molecules are in phase 1 trials and two more will be at phase 1 "soon"

IV. Other Lilly items mentioned of note:

1. Three priorities:
   a. Slowing the sequential erosion of Zyprexa
   b. Focusing on eight new first or best in class drugs
   c. Increasing efficiency and cutting costs
2. New product launches will expand Lilly's sales. Dependence on one product will be minimized (a major theme throughout the meeting).
3. Sales force has increased with partnership agreements:
   a. 2002: 5,300 US sales reps; 14,500 total global sales reps
   b. 2004: 7,500 US sales reps; 17,000+ total global sales reps
4. Ongoing hiring freeze, sales force has been rearranged, expecting $150m savings in 2005

V. Q&A – Jose Caro, M.D., VP, Endocrine Research, and others

1. Answers to diabetes-related queries yielded the following information:
   a. Re: Exenatide: In response to a question on first-phase insulin response, management noted that the FDA has the information on Exenatide's restoration of first-phase insulin response but it would be premature to say what will be included on Exenatide's label. For us, this will be a key area to watch.
   b. Re: Exenatide injections: The injection device for Exenatide LAR will be a pen. Jose Caro, VP of Endocrine Research, commented that physicians may have an easy time convincing patients to go onto Exenatide because of weight issues. In a recent comparison study, Lantus increased weight by 3 lbs. but Exenatide reduced weight by 5 lbs.
   c. Re: DPP-IV inhibitors – the question of weight arose, and management noted that DPP-IV inhibitors generally induce no changes in body weight. The patient population is very different from the population for which Exenatide is considered, Caro asserted. Caro speculated that perhaps the reduced effectiveness of a DPP-IV inhibitor comes from type 2 patients having low levels of GLP-1 to start with. If there's not enough GLP-1 to start with, there may not be enough to induce positive metabolic changes even if the DPP-IV is inhibited. The implication here may be that Exenatide has greater potential and a larger market than DPP-IV inhibitors. We believe it is a greater market, even though it is an injectable, because there are fewer side effect questions, the weight loss benefit looks clearly meaningful (especially at current sustained levels), and the drug could ultimately be used quite early is disease progression.
   d. Re: inhaled insulin: 1) Management asserted that Pfizer will likely be first-in-class with inhaled insulin and that the company has done a lot of work from which Lilly has learned. Notably, management noted that there is no data to support many early safety concerns and said Lilly won't be first-in-class (but posited strong likelihood of best-in-class). 2) Lilly did a 120-patient phase 2 trial comparing inhaled insulin with injections of Regular and Humalog in type 1s. Phase 3 trial being planned now. Caro says Lilly is ahead by having started working on type 1s, but he couldn't say when the phase 3 trial will start or finish.
   e. Re dual PPAR-agonist naveglitazar: Lilly showed phase 2 clinical data on naveglitazar last year; it is doing its oncology study now, and the study will be finished in 2005. As a reminder, the FDA is requiring all companies developing dual PPAR-agonists (outside of BMS and Merck, which just submitted) to conduct two-year rodent studies to assess cancer risk. Phase 3 trial naveglitazar trial is scheduled to start in 2006, *if* everything goes to plan.

Part 2: NIH – "The Role of Insulin in the Critically Ill Patient: Basic and Clinical Evidence," December 9, Bethesda, Maryland

We found this meeting to be an outstanding overview of issues related to basic and clinical evidence for improved inpatient control – a topic that we believe will gain increasing attention in 2005 and beyond... Before this meeting started in earnest, the general theme of potential benefits of insulin usage and improved glycemic control was briefly addressed by the NIDDK. Our main takeaways from the day:

- *The importance of using insulin and monitoring appropriately in the hospital will gain steam and the importance of inpatient control will continue to mount*
- *Implementation is a major challenge (reform, albeit early, has already begun in the US and numerous important thought leaders are behind this drive)*
- *Glucose monitoring automation and glucose delivery are critical to success and winners will be winners big-time, in our view.*
- *Achieving and maintaining glucose levels are* both *critical – the hospital could be a key starting point for ICU and critical care patients in particular*
- *Despite major challenges, the public health implications of improved inpatient glucose control could be tremendous.*
    - *The estimated direct costs of diabetes are $92 billion annually, and a major percentage of this (over 40%) are due to the giant costs of a much smaller percentage of patients who suffer the worst complications (more macrovascular and microvascular complications, longer hospital stays, etc.)*
    - *Although we are very focused on research that will improve control of intensively-managed patients, we also point out that from a public health perspective, far more can likely be saved from shifting a patient's A1C from 12 to 10 than from 7.2 to 6.0 (just an example, but both happen to represent reductions of 17%).*
    - *While we strongly believe that better control in patients is needed across the board, from the perspective of which patients need the most help, we might urge a greater focus on the sickest, i.e., those in the hospital*
- **We saw many star speakers**. Our focus for the day was on clinical rather than basic research and we highlight the following:
- **Greet van den Berghe MD, PhD: Intensive Insulin Therapy in the ICU**[1]. Our conclusions from her talk included:
    - Blood glucose control and insulin work together in reducing mortality.
    - Cumulative effect of treatment are major cause of outcomes such as reduced mortality, but immediate effects are observed, including decreased time to remove tubes, etc.
    - Glucose control alleviates glucose toxicity from insulin resistance in the liver.
    - Insulin itself provides helpful immunological benefits, such as reduced inflammation.
    - There are a number of needs moving forward:
        - Automated glucose monitoring devices (Van den Berghe noted that blood glucose levels in the ICU should be checked every four hours from an arterial line)
        - Nutritional guidelines
        - Expansion of insulin protocols to other patient populations

[1] Van den Berghe authored a highly regarded study in the *NEJM* that helped inspire the entire refocus on inpatient control: Van den Berghe, Greet, "Intensive Insulin Therapy in Critically Ill Patients," *NEJM* 345:19, 1359-1367 (2001)

- **Klaus Malmberg, MD, PhD: Glucose Regulation in Diabetic Patients with Acute Coronary Syndromes.** Comments and conclusions from his talk included:
    - Only one-third of patients in the EURO heart study (25 countries) showed normal glucose tolerance. Reduced glucose tolerance correlated with more cardiac events. Glucose metabolism was shown to have connection to reduced cardiac mechanics
    - DIGAMI 2, a Scandinavian trial, was discussed. DIGAMI 2 had approximately 3000 subjects with diabetes and high blood glucose, or simply high blood glucose (≥11 mmol/L or ~200 mg/dl).
        - Surprisingly, in this trial, patients with diabetes showed mortality rates approaching non-diabetics.
        - Editor's note: We heard the DIGAMI 2 presentation in Munich and will be publishing a longer piece on this in 2005. We are concerned that DIGAMI 2 results may be misinterpreted in the US because: 1) the DIGAMI patient population was in significantly better control than the average type 2 patient in the US; 2) a high percentage of the control group (over 40%) actually took insulin at home, which sort of skews the results; 3) it is unclear whether the treated group took both basal and prandial insulin.
        - We *highly* recommend readers find Dr. Irl Hirsch's piece on DIGAMI "Were We Wrong about Insulin and Acute Myocardial Infarction?" in the ADA's outstanding new journal *DOC*. The text from Hirsch's October, 2004 piece is currently available *gratis* online: see docnews.diabetesjournals.org/
    - Better treatment tools are necessary
        - Simplified insulin treatment (DIGAMI 2 trial used conventional insulin vs. analogs)
        - Use of GLP-1 needs to be studied.
        - Fear of hypoglycemia and lack of expertise are major inhibitors of efficacy.
        - Insulin sensitizers, e.g., PPAR-agonists, should be examined, as they may improve insulin resistance and improve myocardial energy metabolism
        - "*It is necessary to find a 'statin' for glucose*."
        - Although DIGAMI did not show insulin as a factor in reducing mortality in cardiac cases, correlation did occur between glucose control and decreased mortality. "*Glucose regulation is important yet difficult*."
    - Telling Q&A
        - Q: What is necessary to change attitudes towards insulin usage? What is the basis of resistance from cardiologists/nurses?
        - A: Even interested nurses/doctors appear hesitant. We need more efficient insulin delivery mechanisms to produce greater glycemic control. Non-intensive care patients are less receptive to insulin treatment. Dietary control is important as well.
- **Jeremy Cordingley, MBBS: Clinical Experience of Implementing Tight Glucose Control**
    - Length of stay and mortality: increased length of stay correlated with increased mortality.
    - Conclusion: target ranges not reached
    - Fears of hypoglycemia an important factor. Incidences of hypoglycemia had no major consequences.
    - Focus areas for future advances
        - Automation in glucose monitoring
        - Increased nurse and physician education
        - Glucose delivery

- **Anthony Furnary, MD: The Impact of Hyperglycemia and Insulin Infusion on Cardiac Surgery Outcomes: The Portland Diabetic Project.**
    - How does one convince others of the benefits of glycemic control?
        - Stakes: Patients with diabetes are 54% more likely to have cardiac event than patients without
        - Patients with diabetes fare significantly worse: 2x higher morbidity (4.4% vs 2.7%)
    - Hyperglycemia more effectively reduced with IV insulin. (reduction of deep sternal wound infections of 66%, diabetics reaching incidence equal to non-diabetics)
        - Risk of infection increases as hyperglycemia increases – these numbers are quite remarkable:
            - 2x increase @ 175-225mg/dl
            - 4x increase @ 225-250mg/dl
            - 6x increase @ >250mg/dl
    - Total costs savings would approach approx. $500M/year
        - One deep sternal wound infection in a diabetic patient costs $81,000
        - IV infusion reduces incidence from 3.5% to 0.3% (1 such infection per 31 patients) for savings of $2163 per patient
    - Conclusion: length of delivery and glycemic control effective. Focus on duration as well as achieving blood glucose level targets.
    - Q&A of note:
        - Q: Why not more studies, what are some limitations to more studies?
        - A: Great initial resistance. In 1992, initial insulin usage was malpractice. Yet time has changed this conception. More studies should definitely be conducted.
        - Q: Is it wise to return patients to pre-operative insulin protocols when previous protocols were ineffective? Patients often have A1Cs of 11 or 12 prior to surgery.
        - A: More study is necessary. Long-term glucose control is definitely required. Most effective methodology outside of IV administration needs to be developed.
    - *Comment from FDA official*: There is no hindrance or regulatory impediment on behalf of scientists or healthcare practitioners. Companies cannot advocate it because hospital insulin protocols are not approved by FDA for industry discussion
- **Jesse Roth, MD: Summary**
    - On Greet Van den Berghe: described work as "paradigm shift" definitely an important and dramatic movement way from previous thinking
    - On Klas Malmberg: surprised at lack of glycemic control present in Northern Europe. He expected better control than is witnessed in America.
    - On Jeremey Cordingley, MBBS: peaks of glucose, rather than ranges, suggest threshold effect to glucose at maximums rather than at specific ranges?
    - On Anthony Funary: kudos for achievement of reducing diverse affects of diabetic patients to non-diabetic patients. Emerging problem: effects of diabetes as a result of obesity.
    - Roth's own observations
        - Effects of glucose oxidation: effects of glucose of 250 mg/dl are not necessarily bad at the cellular level, but at the organ level they are very serious
        - Inflammation effects of glucose: small effects can have tremendous effects on the brain especially
            - More investigation of effects on brain itself necessary. The brain is a major site of glucose metabolism.

- Possible investigation of inflammatory agents other than insulin, so metabolic and inflammatory effects do not interact.
- Stratify patients in terms of glycemic effects
    - More specific delineation between newly diabetic and those with long history of diabetes
    - More specific targeted approach to glycemic effects
- Target specific regions which lead to mortality: i.e., neurological regions, etc. specific solutions to damage to particular regions
- We must examine long-term effects
    - Why does short-term glycemic control lead to such lasting long term effects?
    - Explore the concept of insulin resistance (cf. Freychet, Smogyi, Gavin, Spigelman, Kahn, etc.)
    - Important point: in addition to primary cause of insulin inhibition, further increases of insulin levels lead to further resistance (hyperinsulinemia)
    - GLP-1 and other agents might reduce glucose levels independent of insulin, thus reducing insulin resistance
    - Noncompliance of caregivers: Colleagues still fail to accept Van den Berghe and others' data; it's necessary to work hard to convince colleagues to accept the importance of glucose control.
    - How far do advantages of glycemic control over a long period extend?
    - Combating fear of hypoglycemia is perplexing, especially among caregivers, despite other dangerous drugs they deal with.
    - Note: it's common to see 40 mg/dl during fasting, etc.
        - It's important to distinguish low levels of blood glucose with over-action of insulin.
        - Possible selling point to reticent healthcare providers.

Part 3: Diabetes Technology, October 30-31, Philadelphia, PA

This was a terrific meeting – we can't review the entire meeting in this space, but note our twenty most items from these few days in Philadelphia included:

1. "*Butt fat is good; gut fat is bad*" – Barry Goldstein quoting Don Chisholm (Garvan Institute, Australia). We couldn't agree more. Intra-abdominal/visceral fat entails a much greater risk for dyslipidemia, insulin resistance, and the Metabolic Syndrome. Plus, doesn't that have a great ring to it?!
2. GLP-1 appears to preserve glucose-dependent insulin secretion in even in patients who do *not* respond to sulfonylureas
3. A speaker from Medtronic noted patients will need to perform SMBG more frequently to confirm alarms with Guardian and claimed that false alarms tend to occur during periods of "glycemic risk," when patients may be trending downward.
4. According to Steve Gutman (CDRH, FDA), the FDA sees continuous glucose monitoring as positive for short-term outcomes and the technology "does appear poised to improve quality of care." We believe the longer-term benefits will be equally important but there is of course no data showing this at this point.
5. Noninvasive technologies to test for glucose and screen for diabetes may be getting stranger than fiction. Contact lenses that change colors according to the glucose level of your tear fluid? Unfortunately, the level of glucose in tear fluid reflects the blood glucose level of a few hours ago.
6. Patricia Mueller (CDC) described the Diabetes Autoantibody Standardization Program (DASP), which aims to standardize lab methods and performance in autoantibody assays. Interestingly, Insulin Autoantibody (IAA) is the most difficult antibody to pinpoint accurately – GAD and IA-2 are much easier. As IAA is useful in typing children, the CDC is keen to improve IAA testing. DASP is collaborating with Pacific Northwest Labs to develop new assays.
7. David Klonoff (UCSF, Diabetes Technology Society) announced that the Diabetes Technology Society is preparing to make some recommendations regarding continuous glucose monitoring so that HCPs will be able to get payors onboard. Great news ~
8. According to Frank Vinicor (CDC), the motto of the Division of Diabetes Translation is "We may not be smart, but we are slow."
9. Steven R. Smith (Lousiana State University) commented that the measurement of lipids *in vivo* is "light years behind" the measurement of glucose. This may be key, as blood lipids become increasingly important to watch.
10. Bruce Buckingham (Stanford) revealed that in a study conducted by Laura Gandrud (Stanford) that on average, toddlers experienced prolonged (~40 mins.) periods of hypoglycemia <40 mg/dl. 1 out of 6 nights. For the greatest utility in the pediatric population, continuous monitors should alarm during long spans of low glucose levels.
11. Philip Raskin (University of Texas Southwestern, Dallas) pointed out that currently 37% of continuous monitors and 71% of conventional blood glucose meters meet the present ADA goal of >10% variance from a lab.
12. Garry Steil (Medtronic MiniMed) described an experimental closed-loop system recently tested on human volunteers. The major complaints? Hypoglycemia after breakfast and 2-hr postprandial hyperglycemia after lunch and dinner. Steil appears confident that these can be worked out, and the data from the trial provide proof-of-concept for external physiological insulin delivery (ePID) and its algorithm. We will be watching closely as this is obviously an area of major interest. Steil says calibration frequency is down to "maybe one a day."
13. Steil nicely summarized the problems of developing an artificial pancreas: 1) glucagon supplementation; 2) hepatic portal vein insulin delivery; slow action profile of subcutaneously administered insulin. In Steil's words, we're trying to take what the β-cell does, modify it, and do

it. Currently, Steil does not believe there will ever be a glucagon-infusing pump outside of a hospital setting – we respectfully disagree.

14. Thomas Vering (Roche/Disetronic) also presented data on a closed-loop system. This system incorporates an external visometric (microdialysis) sensor, a PDA with algorithms programmed in, and an external insulin pump. The sensor follows plasma glucose levels very closely.
15. According to Ben Feldman (Abbott Diabetes Care), the latest data on the Freestyle Navigator continuous monitor suggests 90.9% of Navigator values land in the A region on William Clarke's new error grid for continuous monitors. This compares well to the 90% A-region accuracy of the best conventional fingerstick meters. The average error margin due to lag-time appears to be only 7 mg/dl. Based on rate of glycemic change, the Navigator can detect hypoglycemia faster than a patient unless the patient is checking venous blood glucose levels more frequently than every 25 minutes. Feldman says: "*Lag is a manageable issue*."
16. Jeffrey Joseph (Artificial Pancreas Project, Thomas Jefferson University, Philadelphia lamented the fear of insulin-induced hypoglycemia that often impedes hyperglycemia management in the hospital, claiming that real-time monitoring would help alleviate this. Helpfully, Joseph also pointed out the incongruity in present attempts to calibrate interstitial fluid (ISG) sensors to blood. ISF and blood are not the same, so calibration is difficult. Joseph and his team are modeling meals consumed by type 1s in an attempt to gauge optimal pre-prandial insulin administration time depending on meal composition. Joseph characterized greatest challenge of a closed-loop system as achieving postprandial euglycemia without hypoglycemia. The absence of a counter-regulatory hormone – i.e., glucagon – is another major oft-cited problem, as is the ability to build appropriate algorithms. Still … we're getting there.
17. Judith Fradkin (NIH) described current NIH research/development priorities relevant to islet cell transplants for type 1: inadequate supply; islet engraftment and viability; and immunity. Fradkin said that Camillo Ricordi (University of Miami) has developed a way of counting β-cells on a slide under a microscope so we can gain better knowledge of the numbers. Re engraftment, the vascular nature of islets may be a problem: the cells do not fare well out of their native tissue.
18. On the topic of immunity, Fradkin mentioned less toxic forms of immunomodulation, including islet encapsulation. Fradkin said the NIH hasn't seen as much progress on encapsulation as had been hoped, but two companies now have FDA approval to try it.
19. Andreas Pfeutzner (IFKE Research Institute, Mainz) raised a scintillating prospect: proinsulin as a cause of insulin resistance. As general beta cell function deteriorates in type 2 patients, an increasing proportion of the insulin secreted is not truly insulin but proinsulin. Pfeutzner suggested that the increased risk of CVD from sulfonylureas might originate in the stimulation of proinsulin, because exogenous proinsulin is an independent risk factor for MI and CVD. Pfeutzner said pioglitazone (Actos) reduces intact endogenous proinsulin (fascinating!). He argued that measurement of fasting intact proinsulin secretion might be useful in deciding when to change therapies for type 2 patients.
20. Jacob Sten Petersen of Novo Nordisk discussed Novo's latest insulin analog, detemir (Levemir). Petersen emphasized the safety of detemir throughout his presentation and also potential weight-neutrality.

One of our favorite parts about the Diabetes Technology meeting every year is the interactive survey held among attendees at the very end – fabulously interesting!

1. Which of the following diabetes-related technologies deserves more investment from funding research agencies?
- Blood glucose sensors 39%
- Inhaled, oral, buccal, and nasal insulin 1%
- Novel transdermal insulin delivery systems 34%
- IT solutions (including telemedicine) for the management of type 2 diabetes and of the metabolic syndrome 22%

2. Which is the most appropriate type of glucose sensor to be used in a closed-loop insulin delivery system?
- Subcutaneous (needle-type) 34%
- Subcutaneous using microdialysis 9%
- IV 26%
- Percutaneous sensor using reverse iontophoresis 1%
- Non-invasive sensor 30%

3. What are the most appropriate type and route for insulin infusion to be used for closed-loop?
- Regular by subcutaneous 11%
- Fast-acting by subcutaneous 38%
- Regular by IV10%
- Regular by intraperitoneal 16%
- Fast-acting by intraperitoneal 16%
- Combination of Regular or fast-acting plus inhaled 9%

4. How developed should a full closed loop be before commercially available?
- Full 24-hr 20%
- Night-time only 14%
- For patient's selected time periods 14%
- For basal insulin needs and patient self-adjusted bolus to meal time/size 43%
- For basal needs and patient self-adjusted bolus to meal size only 10%

5. The most important bottleneck in developing near-infrared spectroscopy as a non-invasive glucose sensing tech for routine use in diabetes?
- Difficulty in miniaturization of tech 7%
- More funding needed for development 7%
- Calibration is too complicated 6%
- Specificity is poor 36%
- Tissue physiology is poorly understood which interferes with interpretation of signal 46%
- Technology is incapable of meas. glucose 0%

6. Most important drawback of presently available continuous glucose sensors based on subcutaneous implanted needle-type enzyme electrodes?
- Need for freq calibration 24%
- Duration of use for each sensor limited to a few days 29%
- Inaccuracies of readings 25%
- Difficulty of interpreting continuous data 5%

- Insufficient evidence for clinical benefit to patients 9%
- Poor patient acceptability 7%

7. What will be necessary to convince healthcare payers to pay for inhaled insulin if this product receives approval of FDA?

- More pharmacokinetic and pharmacodynamic data 1%
- More clinical outcome data that inhaled achieves control as good as or better than subcutaneous insulin 27%
- More Quality-of-life data showing that patients failing oral agents prefer to use inhaled instead of subcutaneous insulin 7%
- More data on safety issues 21%
- More pharmacoeconomic evaluations showing clear benefit if inhaled insulin is used 31%
- Large co-payment 14%

8. Which of the following IT based interventions could be most cost-effective?

- Shared electronic records to be used by entire healthcare team 12%
- Telemedicine for home care, able to periodically transmit data from home to diabetologist/case manager 20%
- Decision support system for primary and secondary care healthcare professionals, providing electronic guidance 11%
- Multifunctional systems for disease management by entire team providing data sharing, second opinion consultation and 2-way patient/caregiver communication 32%
- Patient-tailored educational and decision support systems embedded in PDAs and other portable devices 25%

9. Given society's limited resources, which of the following possible therapeutic approaches for type 1 diabetes should be pursued most actively with public funds?

- Cell-based therapies using autologous cells 5%
- Cell-based therapies using allogenic cells including stem cells 33%
- Gene therapy for reversal of IDDM 5%
- Gene therapy for early detection & prevention of autoimmune beta cell attack 21%
- Immune therapy to blunt or prevent the autoimmune destruction process 15%
- Bioartifical pancreas 22%

Part 4: Earnings reports of note
Most of the earnings news was out in our last issue, but here are a few extras:

I. Novo Nordisk 3Q04

1. **Novo Nordisk had much news in its third quarter report** – with three major items in our view. First, growth continued strong in the core insulin business. Overall diabetes care revenues increased by 11% (in Danish Kroner [DK]), while insulin analogs grew at an 80% year-over-year clip. Second, Liraglutide (NN2211) was delayed by at least one year. Due to unspecified "non-clinical findings", Novo will conduct a 170-patient Phase 2b study. This will push the Phase 3 study back to late 05/early 06 and could push back approval to 2008. Third, Novo discontinued Balaglitazone outright. Due to insufficient efficacy, Novo has pulled the plug on this PPAR-gamma drug.
2. **Growth in the insulin business remains strong**. Novo reported total diabetes care sales of 14.97 billion DK (approximately $2.6 billion) for the 9 months ended September 30 – up 11% over last year. Insulin analog sales came in at 3.2 billion DK (approximately $550 million) – up 80%; human insulin sales at 10.5 billion DK ($1.8 billion) – down 1%; oral medications at 1.25 billion DK ($215 million) – up 19%.
3. **Sales boosted** by increases in US. wholesaler inventories to the tune of $100 million. Sales to North America were about 27% of the total and North America was identified as the primary growth driver for Q3 results.
    - Novo management believes that its share of insulin analogs is now approaching 30% and analogs are now 20% of all sales. Going a step further, total market penetration of analog insulins is now at around 34%. Management believes it has roughly 20% insulin market share in the United States, and close to 20% of the U.S. market for analogs. What's more, analogs are close to 50% of Novo's total N. American sales. Novolog/NovoRapid has roughly 40% share of short-acting analogs and NovoMix has roughly 43% share of pre-mixed analogs.
    - Growth in Europe was hampered by increasing government concerns with cost reforms, while growth in Asia was fueled by NovoRapid and NovoMix 30. In developing counties, Novo Nordisk has become the leader in analog sales and human insulin sales have been a strong driver in China and Brazil.
    - Growth in the sale of oral diabetes medication was fueled largely by the US, where increases in wholesaler inventories and higher prices have boosted results.
    - U.S. growth has been slowing**.** While sales in the U.S. are boosting Novo's results, management acknowledged that U.S. market growth has been slowing. Management believes this is due in part to Glucophage ER and that normal growth should resume next year.
    - Mixes are still a key part of the future**.** Despite the slower acceptance of Novo's pre-mixed insulins, the company maintains its belief that NovoMix will become its biggest product. Management believes that the success of Lantus has delayed conversion to mixes, but that type 2 patients will ultimately demand better control and look to achieve it through mixes.
4. **Levemir is beginning its journey**: Despite a very limited rollout in Europe, Levemir ended the quarter with 3% of the European market for long-acting insulin. Thus far, Levemir has been launched in 10 countries and the drug has 10% share in Switzerland, 4-5% in the UK, and 13% in Germany. Looking ahead, management expects Levemir to be a major growth driver for its European sales.
    - Management believes it has tied up the remaining regulatory issues with Levemir in the United States and the company plans on filing an amended NDA before year-end. The company expects approval some time in the third quarter of 2005, but gave no details regarding an expected launch date. Of note, the facility that will manufacture Levemir for the United States is currently under construction, so the regulatory path for Levemir involves more than just the NDA.

5. **Pipeline – Big news regarding Liraglutide and Balaglitazone**
    - Liraglutide will see at least a one-year delay**.** Novo has announced that it will conduct a supplementary Phase 2b trial with 170 patients. This study is being conducted due to unspecified "non-clinical findings" seen in non-human (presumably rodent) studies. Plans for this study apparently came about as a result of discussions with the FDA concerning the progression from Phase 2 to Phase 3 studies. This study will commence in 2005 and Novo hopes to follow this with a 3,500-patient Phase 2I study in late 2005/early 2006. This new trial pushes back the timeline by at least a year and suggests that the company will not be able to file for US approval until 2008. Interestingly, Novo has only conducted one trial to date with a full clinical dose (2mg), which lasted only 5 weeks. We believe it is fair to suggest that there is still a lot left to learn about this compound. While Novo Nordisk management maintains that this study will remove a great deal of the risk from the Phase 3 study, we would point out that the drug has to pass Phase 2b before Phase 3 becomes a major concern.
        - What are "non-clinical findings"? Management refused to specify exactly what issues are to be addressed/studied in this Phase 2b study, but strongly asserted that they have not been seen in "near-human" studies and that they do not expect to see them in human studies. Recruitment for this trial should be interesting – we are not sure how easy it will be to recruit for a drug study where the compound is experiencing side effects in animal studies problematic enough to postpone a Phase 3 study.
        - In our view, this news represented a major boost for Amylin and Exenatide. With this delay, Amylin looks to have a nearly three-year head start on all of its would-be GLP-1 analog competitors. It's impossible to say now whether this three-year lead for Amylin will be insurmountable, but we do believe it will be significant.
        - Novo management made a couple of interesting observations in discussing the Liraglutide delay. First, the company is uncertain as to whether these drugs will have a meaningful impact on insulin sales – although it's conceivable that effective new drugs will delay the progression to insulin, that is not yet known with any certainty. Also interesting, Novo believes that the beta-cell restoration effect seen in many GLP-1 analog studies may be a more or less moot point – according to Novo management, proving beta-cell restoration in human trials will be a "nightmare" and its unclear if anybody will be willing to tackle that sort of challenge just for a boost to their labeling. We respectfully disagree and believe beta cell preservation interest will continue to be big, although obviously studies remain both small and early.
    - Balaglitazone – the end of the road. As noted, management announced that it was discontinuing development of Balaglitazone due to "inadequate preclinical results." Balaglitazone was to be a PPAR-gamma agonist and was in Phase 2 studies. Given the fact that there are already PPAR-gamma drugs on the market and everybody is eager for the new dual-PPAR-agonist drugs (assuming they pass extended safety/toxicity studies, still a major if), this is probably a wise conservation of resources for Novo Nordisk. Without compellingly better data, Balaglitazone would have been doomed to become an "also-ran" that would have been hard-pressed to earn back its development costs.
    - AERx – There was no news reported on the AERx inhaled insulin project. The pharmacokinetics/pharmacodynamics study is ongoing and expected to be completed in the first half of 2005. Readers should recall that Novo Nordisk recently acquired total responsibility for the project from Aradigm – something we feel they likely wouldn't have done unless they were significantly committed to the project.

II. Sanofi-Aventis 3Q04

1. Long acting insulin analog Lantus continues on a roll, showing no signs of a slowdown, and it will be very interesting to see how growth changes once Novo's Detemir is approved in the US. No word on that timing – Detemir may have weight advantages, but real world use remains to be seen. Aventis is enjoying longer-than-expected absence of a 24-hour insulin than it had expected and marketing continues strong. Though Detemir is said to be doing well in Europe, Lantus growth there remains robust there as well.
2. Sanofi Aventis reported revenues for Lantus of 224M Euro for Q3, up 85%. Lantus grew 67% in the U.S. (137M E) and 116% in Europe (72M E). Estimated US market share was 25% during Q3, remarkable growth since its launch in late 2000. 9-month results for Lantus hit 599E – the compound is now Sanofi's eighth largest drug.
3. Amaryl, an Aventis oral drug, achieved revenues of 161M Euro; up 9.5%. This drug, which has been oft-marketed with Lantus as "*one shot a day/one pill a day*" grew 12% in the U.S. (47M E), 6% in Europe (58M E). We do question this marketing since we believe many type 2 patients that are not on prandial insulin in addition to basal insulin *should* be. Will be fascinating to watch how this marketing changes with Aventis' new rapid acting insulin coming on the market shortly.
4. A major focus on the call was inhaled insulin and whether Pfizer wants to change the agreement among Pfizer/Aventis/Nektar regarding the drug – lots of speculation now that Aventis is owned by Sanofi. Apparently Pfizer is debating whether to keep it or buy it (or possibly sell it to Sanofi). At present, each company has designated a banker to evaluate and value the product. Sanofi is in disagreement with Pfizer over whether the Aventis acquisition involves a change of control that gives Pfizer the option to buy the entire program from Sanofi/Aventis.
5. Sanofi was cagey, and didn't appear overly eager on Exubera, noting that the company is "*considering its options*." It refused to confirm that it really wants Exubera, noting that the compound is "*charming at first glance*," but that they believe that market access/potential is far more questionable. To what extent is the European healthcare system ready/willing to pay for something that's "essentially the same, but much more expensive"? A different question – what would the public health implications be, given that costs for complications are so giant?
6. There was one question on plant ownership for Exubera – right now it's considered to be co-owned by Pfizer and Sanofi. The plant would go with the product rights. The timing of the court decision wasn't clear.
7. Lots of (endless) discussion ensued about integration of Aventis and how/when/why they're going to report blended results – consolidation occurred September 30, so the 9-month results do not include Aventis, though they did give Aventis results.
8. There was a bit of news on Apidra, or Gluycine, the company's new rapid-acting insulin that was approved in April in the US and that will compete with Humalog and Novolog. The company has now submitted Apidra for approval with the new OptiClik reusable pen system in the US (filed September 30). This is another example of drug/device convergence, as we believe they may launch this insulin in a pen formulation only. Approval of Apidra was announced in Europe on October 4, and is being marketed as a complement to Lantus. As noted, it will be fascinating to see how marketing for Amaryl change. Stay tuned on this front!
9. Sanofi Aventis also gave no update for Acomplia, or rimonabant, its drug in Phase 3 that is aimed at helping people both lose weight and quit smoking. Concerns remain about side effects. Currently there are seven Phase 3 trials that are part of two clinical development programs. We believe Sanofi will file for approval in 2005, making launch in 2006 potential.
    a. RIO (Rimonabant in Obesity) has over 6600 obese patients in the US, Europe, and elsewhere worldwide in four phase 3 studies examining a range of indications including 1) obesity management; 2) prevention of body weight regain after prior weight loss; and 3) improvement in obesity related risk factors in patients with obesity, diabetes, and/or dyslipidemia. In particular, one one-year study, RIO-DIABETES is of particular interest

to us, since the population, over 1,000 patients, has type 2 diabetes. The studies range from one to two years in length.

b. STRATUS (Studies with Rimonabant and Tobacco Use) has over 6,500 patients in Phase 3 trials in the US and Europe testing indications associated with smoking cessation and long-term abstinence, reduction in tobacco use, and prevention of weight gain upon smoking cessation.

10. At both EASD and NAASO (obesity meeting in Las Vegas last month), Sanofi did a superb job in our view of pre-marketing (er, educating) healthcare professionals on the endocannabinoid system (cannabinoid receptors and their natural ligands). Sanofi believes that the EC System, as they have taken to calling is, plays a key role in regulating body weight and glucose and lipid metabolism and also plays a role in tobacco dependence. They explained in their symposia that ECB (endocannabinoids) bind to and activate the cannabinoid (CB) receptors – CB receptors are apparently found in the brain and in some peripheral body tissues, including adipocytes that are related to lipid and glucose metabolism. The company says that through central and peripheral activity, the EC system works on satiety, helping regulate food intake and energy output.

III. Merck Q304

1. Merck noted that it expected Muraglitazar to be filed in the fourth quarter of 2004, and indeed it was, on December 23, as noted earlier. As a reminder, Merck is BMY's partner on the dual PPAR agonist that is positioned as beneficial both in terms of glycemic and lipid control. BMY formed the co-promotion for this drug with Merck earlier this year.
2. Responding to a question on Muraglitazar, the company said the threshold of necessary toxicity data had been passed – it was unclear whether they were referring to human toxicity studies as well as mouse studies but we assume both if they are about to file.
3. MK431, Merck's DPP-IV inhibitor, is in Phase 3 trials and it expects to file for approval in 2006

IV. Becton Dickinson

1. Blood glucose monitoring revenues for the quarter came to $15 million, and $42 million for the year.
2. BD has sold blood glucose monitors exclusively in the US. The market is just over $2 billion of which they have $40 million. They continue to believe that the best way to focus their resources is to focus on high users. In the first years of launch they are focusing their efforts on frequent insulin injectors and pump users (25% of the type 1 population with diabetes). They are engaged in direct-to-consumer advertising and will be significantly increasing DTC marketing this year. However, they believe they can reach their target segments more effectively than through television advertising. They will begin broadening their efforts with people with type 2 diabetes as well.
3. The FDA has granted clearance for alternative site testing for blood glucose monitors. However, BD has not built in an expectation of significant ramp up associated with this recent claim (claim says palm testing is equivalent to finger testing). They believe most people will still test on the finger and do not think this is a market mover for BGM.
4. Overall worldwide diabetes care revenue totaled $155 million, up from $152 million a year ago. representing an increase of 2.2% (FX neutral (.1%); FX impact 2.2%)

V. Alkermes

1. Alkermes expressed excitement about its "emerging diabetes franchise," which it characterized as being at the forefront of developing convenient therapies to help control blood glucose levels.
2. Management appeared to be pleased with its collaboration with Lilly. As a reminder, in late August, Alkermes announced that Eli Lilly decided to proceed with significant investment for the further development of an inhaled formulation of insulin. This was due to the successful execution of specific steps, including the completion and analysis of data from a phase 2 study, the achievement of

commercial manufacturing powder production scale up, and the development and testing of the commercial pulmonary insulin inhaler system.

3. In November 2004, Alkermes, Amylin, and Lilly made the decision to initiate a Phase 2 multi-dose study of exenatide LAR (long-acting release) in type 2 diabetes patients using a once-a-week dosing regimen. This will be incredibly important for determining the opportunity for a long acting formulation of exenatide and is expected to begin in the first quarter of 2005.
4. Data from the ongoing Phase 2 single-dose study have demonstrated sustained release of exenatide with no dose-limiting side effects.

VI. Nektar

1. Management asserted it is making progress with Exubera (inhaled insulin in development with Pfizer and Sanofi-Aventis) – Pfizer announced earlier this month Exubera would be filed for FDA submission in 2005.
2. Management noted that Pfizer and Sanofi-Aventis presented encouraging 2-year data at EASD, showing sustained blood glucose control and pulmonary function for 2 years in patients with type 2 diabetes.
    - The data presented at EASD were from a prospectively randomized trial extended from 6 months to 2 years in which the primary objective was to determine long-term pulmonary safety.
    - After 104 weeks, there was no significant difference between the Exubera (inhaled group) and oral group. During the 2-year period, patients in both groups experienced declines in pulmonary function compared to baseline. Small pulmonary function differences between the two groups occurred early after treatment initiation. However, these differences had no identified clinical relevance and did not progress with two years of continued inhaled insulin treatment. We will look forward to longer term data.
    - Efficacy was demonstrated by reduction in hemoglobin A1C levels in the Exubera group.
    - An analyst asked whether this data was sufficient to answer the safety question – management responded that Pfizer must answer that question.
    - Another analyst asked for more information on the issue that the Committeee on Safety of Medicine in Europe had with this study – again, the speaker wouldn't comment – said that they would defer that question to Pfizer.
    - Pfizer and Sanofi-Aventis submitted Exubera for review by the European Medicines Agency (EMEA) for marketing approval in the European Union in February 2004. According to Pfizer, interactions between Pfizer and Sanofi-Aventis with the European regulatory authorities are ongoing.

VII. Polymedica

1. As a reminder to those that don't watch this company closely, PolyMedica is medical products company best known through its Liberty brand name and direct-to-consumer television advertising to seniors with diabetes. The Liberty diabetes business segment provides lower-cost diabetes supplies and related products and services directly to the rapidly growing population of Medicare-eligible seniors with diabetes.
2. Liberty Diabetes segment net revenues for the quarter were ~$77 million compared with ~$71 million for the same quarter 2003 – this represents about 69% of consolidated revenues for the quarter and a run rate of over $300 million.
3. Polymedica routinely gives various stats on its calls – the one of interest this time was that the incidence of diabetes in the U.S. population age 65 or older was 20.1% in 2000 compared to 18.4% in 1999. This isn't new news, but it certainly gives one pause, considering aging of the population, the progressive nature of diabetes and the fact that treatments are improving, so more people live longer lives. That's good, in some respects, though the fact that more complications ensue (that in earlier years would have represented final straws) obviously has a negative impact on costs.
4. Reimbursement notes of interest: As noted last issue, we will start to look at the Medicare Modernization Act and its impact (mostly on price) in more depth shortly – we recently interviewed expert Bob Knorr on this front. On a related note, Polymedica noted that reductions in reimbursement rates for diabetes business were expected to take place in March quarter – diabetes test strip reimbursement rates will be reduced by roughly 3%. So 3% - that's not that big, it would seem but c'mon, 3% - if the US market is $3 billion (which it may not be, quite, but for easy math), that's $90 million cut out of the market right there! $90 million – said another way, six times the amount Bush initially offered to send Asia. That's not so small. Polymedica forecast this could have a negative impact of as much as 5 cents per share. Polymedica said efforts were underway to appeal this reimbursement reduction – we think pricing on this front is going one direction only.
5. Customer acquisition up: The company's active diabetes patient base is 654,000 representing an 11% increase over last year's 2nd quarter patient base, but still down in terms of plan for the year. Management mentioned that as the company grows, it will be critical to attract patients in larger blocks by expanding relationships with insurance companies and large corporations. It is aggressive in terms of goals as it aims to increase its diabetes growth rate back to a 15-20% run rate. Even though demographics are good, we think this is aggressive.

Diabetes Close Up is a newsletter highlighting notable information and events related to selected companies with diabetes/obesity businesses. This newsletter is put forth as an unbiased commentary on the industry. If you have any suggestions or comments regarding content, please contact info@closeconcerns.com. If you would like to 1) unsubscribe; 2) receive a monthly digest rather than real-time updates; 3) add a name to the DCU mailing list; or 4) offer any suggestions or comments regarding content, please write to info@closeconcerns.com.

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