JP Morgan 29th Annual Healthcare Conference January 10-13, 2011; San Francisco, CA Full Report - Draft

Executive Highlights

As in years past, the 29th Annual JP Morgan Healthcare Conference provided us with valuable updates on activities within the diabetes and obesity industries. Out of the 350+ companies and organizations in attendance, we bring you our coverage on over 50 diabetes- and obesity-related companies. Below, we start with our high-level themes for the conference, followed by detailed commentary from company presentations (listed in alphabetical order). As always, it was great to catch up with so many of you in San Francisco, and we thank JP Morgan for its enormous continued commitment to the life sciences.

- **In contrast to past years, this year's JP Morgan Healthcare Conference had a seemingly constant flow of new updates for diabetes- and obesity-related companies in attendance.** Notable news included the Eli Lilly/Boehringer Ingelheim strategic alliance, Dexcom's pre-release of better-than-expected 4Q10 financials, Biocon's first look at the Indian phase 3 data for oral insulin IN-105, the filing of Bristol-Myers Squibb's SGLT-2 inhibitor dapagliflozin in the US and the EU (a big deal), the advancement of glucokinase activators by both Array BioPharma and Forest Laboratories into phase 2 studies, the announcement by Halozyme of the initiation of a phase 1 insulin pump study with PH20, and additional guidance from Biodel regarding its ultra-rapid acting insulin program. Overall, while these new developments were unexpected with full-year 2010 results following shortly after the conference, we were glad to see so much ongoing activity in the diabetes and obesity arenas, and we left excited for what should be an eventful 2011.
- **Eli Lilly announced a major partnership with Boehringer Ingelheim (BI), while sanofi-aventis emphasized its own broad commitment to treating diabetes.** Lilly and BI revealed that they are co-developing and co-commercializing two of BI's oral drugs for type 2 diabetes (the already-FDA-submitted DPP-4 inhibitor linagliptin and a phase 3 SGLT-2 inhibitor), two of Lilly's phase 2 basal insulin candidates (a novel analog and a glargine product that will be released in a new, unspecified delivery device), and potentially a phase 2 Lilly drug for diabetic nephropathy. Lilly now has arguably the industry's most comprehensive late-stage pipeline: as Lilly Diabetes President Enrique Conterno put it, "we could become the premier diabetes company in the world." This statement recalls the we-want-to-be-number-one rhetoric of sanofi-aventis CEO Chris Viehbacher last year, who at this year's meeting highlighted his company's own efforts to expand the way it addresses diabetes. The company continues to branch out with its AgaMatrix-partnered, iPhone-compatible blood glucose meter the iBGStar, which Viehbacher announced will be available at Apple Stores. sanofi-aventis is also looking with interest toward efforts at patient education and prevention programs, particularly via mobile devices. Meanwhile Novo Nordisk continues, like sanofi-aventis and Lilly, to increase the depth and breadth of its own diabetes treatment efforts - though unlike its rivals, the Danish company does not present at the JP Morgan Healthcare Conference, citing the "quiet period".
- **Activity and interest in the diabetes complications arena are on the rise.** Reata's lead compound, bardoxolone methyl, demonstrated significant promise as a treatment for chronic kidney disease (CKD) in people with type 2 diabetes in a recent phase 2b study. The companyintends to initiate a 1500-patient phase 3 trial in 1Q11 expected to complete in 2H12; this would enable Reata to launch bardoxolone methyl as early as 2013, assuming favorable regulatory review. We note that this compound has already garnered significant (we would say remarkable) interest - Abbott gave $450 million in upfront and near-term cash payments to Reata for exclusive rights to develop and

commercialize the drug outside of the US (excluding some Asian markets). Meanwhile, Sangamo Biosciences' diabetic neuropathy candidate SB-509, has the potential to be a "first-in-class, disease-modifying drug," as it promotes nerve regeneration and has the potential to halt and reverse the progression of further nerve loss by activating transcription of VEGF-A, an important growth factor implicated in both neurogenesis and angiogenesis. Results from the phase 2b study (901) for SB-509 are expected in 2H11. On the diabetic macular edema (DME) front, a number of candidates were highlighted at JPM this year: in 2Q09, Allergan completed phase 3 enrollment for Ozurdex, and expects to receive FDA approval for the indication in 2013 or later; Regeneron is in the planning stages for phase 3 studies for the use of VEGF Trap-Eye to treat DME; and sanofi-aventis has a bradykinin B1 antagonist (FOV2304) currently in phase 2 studies for the treatment of DME. In addition, sanofi- aventis also has a long-lasting urotensin II antagonist for the treatment of diabetic neuropathy (SAR101099; phase 1). As patients stay older longer due to better drugs, they will develop more complications that need to be treated - we are spending a lot of energy this year trying to better understand these.

- **There were several updates on the device front, after regulatory setbacks in the US have delayed the timelines for next-gen CGMs, pumps, and combined pump/CGM products.** In particular, Dexcom announced that it would conduct trials of its fourth-generation sensor in late 1Q11 or early 2Q11 and begin trials of the combined Dexcom/Animas product immediately thereafter. As a reminder, the fourth-gen sensor will be 50% smaller by volume, more accurate due to new membrane technology (especially in the hypoglycemic range), and less susceptible to interference from the immune system. A slew of improvements has been typical for each new generation of Dexcom sensor and we doubt there will be disappointment on this front with this next-gen. In a trend we're beginning to see throughout the industry of predicting approval in the EU before the US, both the fourth-gen sensor and the Dexcom/Animas combination product are expected to launch in Europe in the first half of 2011, pending favorable regulatory reviews. As for the Insulet/Dexcom combined pump/CGM product, there was some uncertainty surrounding the versions of each component product that would be included in the combination. As we understand it, the decision is between combining Insulet's current pod and the third-generation Dexcom sensor (the combination that was originally submitted) or Insulet's next-generation pod and the fourth-generation Dexcom sensor. In general, both Dexcom and Insulet provided extensive updates on their businesses and vision for the upcoming years although trying to work out how the two companies were working together in terms of exact product specs was challenging.
- **While there were no major updates on the obesity products, we gained additional perspective on the clinical program for pramlintide/metreleptin (Amylin/Takeda) and the regulatory approach for Qnexa (Vivus).** Notably, we learned during discussions with Takeda management that Amylin/Takeda are currently conducting studies on new co- formulations of pramlintide/metreleptin in an effort to develop a twice-daily, or even possibly once-daily, injection for the combination therapy (four injections per day were used in the previously conducted phase 2 trials). We were glad to see Amylin/Takeda move forward on this front, since we believe the number of injections must be reduced for this combination therapy to be a viable compound for the treatment of obesity. For the obesity drugs that have receivedcomplete response letters, the breakout rooms focused solely almost exclusively on the companies' regulatory approaches and commercial expectations. Specifically, Vivus management clarified that they would not propose a limited indication with respect to cardiovascular safety and they plan to launch in the US itself (without a partner). Lastly, we note that the recent news of Orexigen's complete response letter requiring a pre-approval outcomes study only came after the JP Morgan Healthcare Conference.
- **For numerous companies (both inside and outside the diabetes arena), emerging markets are becoming the key area of focus to drive growth.** Notably, Eli Lilly management highlighted its increased investments in China, as a significant market opportunity exists - according to management, the insulin market in China right now is $400 million, and is expected to increase tenfold in the next five to seven years. Our recent trip to China reinforced to us

the importance of the area and we hope very much that we can continue to watch this closely; to date, the visibility of Novo Nordisk's and Eli Lilly's businesses there has been very welcome. Meanwhile, Merck CEO Ken Frazier noted that over 75% of the worldwide diabetes population resides in developing markets, and he hinted at the company's intent to expand its presence in those markets. In addition, Takeda emphasized its efforts to "achieve globalization," emphasizing its plans to focus on India, Australia, and Russia in the near future.

- **There were very few private companies presenting at JPMorgan this year - we report on Intuity Medical and Reata and Intarcia - hard-won places, and great credit to these companies for winning these spots. Nonetheless, we did also see three other private companies during the week of JPM this year. At OneMedForum, the smaller meeting that takes place alongside JPM, we also had the chance to receive quick updates from CeQur and Dance Pharmaceuticals, while we also saw D. Medical during the few days of the JP Morgan meeting.** CeQur CEO James Peterson presented and showed they had done some good thinking about type 2 patients and pumps. We look forward to learning more going forward; it seems the company may well have an advantage on the COGS front. There are certainly more than enough type 2 patients who need help with insulin to work with; we believe that although insulin pens have been highly successful, there are still millions of type 2 patients in the US alone failing oral therapy and not moving to insulin. Although some are taking GLP-1 (and we believe even more will be going forward), beta cells won't last forever and there is a major unmet need for good solutions for taking prandial and correction doses in addition to long-acting insulin. We think Valeritas and CeQur both have big potential to help patients on the insulin delivery front, as does Calibra - as long as all are easy to use, all have major potential to help on the adherence front, which is the major problem in our view. Like Valeritas' A Team, CeQur also has some very strong executives, including the Chairman of its BOD, Eric Milledge, former head of LifeScan. Also presenting at OneMedForum was Dance Pharmaceuticals CEO John Patton, former head of Inhale/ Nektar. He is looking to bring back inhaled insulin in a better application; while the MannKind delays haven't helped, they have a strong point that more and better alternatives are needed for patients with type 2 diabetes. There is also interest in inhaled insulin used as a chaser for type 1 patients, although this was not discussed. Last, we got to see D. Medical's next pump; this was very small and looked cool and we're looking very forward to learning more about this - we believe expanding the pump market has just begun and that with cooler options for patients, as long as costs are reasonable, penetration could climb steadily higher, especially in areas outside the US. We also believe the US penetration among type 1s could reach 40-50% in time, with improved patient options - smaller, with CGM, cooler, sleeker, more communicative - and in type 2s - simple is the word there.

Detailed Discussion and Commentary

Company Presentations

ABBOTT

Thomas Freyman (CFO, Abbott, Abbott Park, IL)

During Abbott's presentation, CFO Thomas Freyman provided no new updates on Abbott's Diabetes Care business. Although certainly not a primary focus for the company, we were still disappointed that this business was only briefly mentioned during an overview of Abbott's medical device products. Instead, Freyman spent most of the presentation focusing on Abbott's pharmaceutical pipeline, nutritional products division, diagnostics division, and expansion into emerging markets. During the breakout session, there was also very little interest in the Diabetes Care divisions with just one question addressing the recent blood glucose strip recall, overall performance of the division, and future plans for the division. Somewhat unsatisfactorily, although management indicated that they did plan on retaining it, they failed to provide any guidance on their future plans for the division. With regard to the strip recall, management appeared to view it as a minor event with little to no financial impact on the company. As a reminder, this past

December Abbott decided to voluntarily issue a recall of 359 lots of blood glucose strips (i.e., roughly 359 million strips) from several Abbott brands (Precision Xceed Pro, Precision Xtra, Medisense Optium, Optium, OptiumEZ and ReliOn Ultima) after discovering 22 falsely low measurements with these strips through the company's own quality control testing. We were glad to learn at the time of the announcement that that this does not relate to its main business, the FreeStyle strips; as well, as we understand it, Abbott identified this issue through routine, internal quality processes and then initiated an investigation. We will try to stay abreast of FDA response; while we have long since finished trying to forecast what the agency will do on any front, the company does appear to be approaching this very proactively.

Questions and Answers

Q: In regards to your diabetes unit, can you comment on the recent recall of some of your test strips? Also, the unit hasn't performed all that well of late. Can you comment on what your future plans are for the unit? Are you planning on dropping it at all?

A: Yes, we plan on keeping it. Our recent focus on individuals using multiple daily injections has caused a substantial improvement in profitability and has allowed us to access certain channels in the marketplace. Right before Christmas, we did issue a recall in the US. We are in the process of bringing the product back. We want to manage these cases in the best interest of patients. There have been some challenges in the Diabetes Care business as of late, but in general we are taking an interest in this business and we see sustained growth coming from this business over time. The financial impact of the strip recall was very minimal; it was more of a rounding issue from an added perspective.

ALKERMES

Richard Pops (President and CEO, Alkermes, Waltham, MA)

In one of the opening presentations of the conference, CEO Richard Pops provided a valuable preview of expected developments for Alkermes in 2011 as well as a review of 2010. While most of the presentation and the following breakout session focused on the newly approved opioid dependency indication for Alkermes' Vivitrol, some attention was paid to the company's once-weekly GLP-1 agonist Bydureon under development with partners Amylin and Eli Lilly. Mirroring much of what was said by Amylin CEO Daniel Bradbury in a presentation later on in the day, Pops spoke confidently about the compound and appeared reassured that despite the FDA's recent (second) complete response letter for the drug (see October 20, 2010 Closer Look), Bydureon would eventually gain regulatory approval in the United States given its demonstrated safety and efficacy. Amylin recently submitted a protocol for the requested tQT study to FDA and expects to initiate that trial in 1Q11 with the goal of resubmitting Bydureon to the FDA before the end of 2011. Bydureon was also submitted in the EU by Eli Lilly in the spring of 2010, and action by the EMA is anticipated in the first half of 2011. Pops underscored his belief that Bydureon should be quite a successful product - in his view, patients will be attracted by the demonstrated efficacy and tolerability, once-weekly dosing, and lack of required dose adjustments; providers will be attracted by the unit dosing, simple directions for use, and minimal training; and payors will be attracted by the extensive claims data thus far for Byetta and head-to-head efficacy data from the DURATION trials with other anti-diabetic compounds. Eventual pricing of Bydureon remains a question; many expect it to be sold at a premium to Byetta, and results from the DURATION-6 trial (which Pops indicated would report in 1H11) that compares Bydureon head-to-head with liraglutide (Novo Nordisk's Victoza) may impact the degree of success Bydureon achieves with payors. We do think that although liraglutide is seeing demand among providers, the "high dose" is experiencing acceptance issues with some payors (the 1.8 dose is approximately 50% higher in price than the standard 10 mg dose of Byetta). Finally, Pops provided a quick update on the development of Amylin/Eli Lilly/Alkermes' exenatide once-monthly suspension (no reconstitution necessary) and indicated that phase 2 results for the compound are expected in the first half of 2011 (NCT01104701).

- **Pops stressed that Alkermes stands to profit substantially from Bydureon sales in the future.** Although approval of the drug has been delayed and the FDA has requested an additional study, this comes at no cost to Alkermes outside of foregone royalty income from Bydureon sales. (The company is not responsible for any further costs associated with the commercialization or

regulatory filing of the drug in any territory.) During today's presentation, Pops provided additional details on the royalties Alkermes stands to receive from US Bydureon sales. During the growth phase, in which the operating margin is expected to be 25%, Alkermes will receive 32% of the profit, Amylin will receive 34% of the profit, and Eli Lilly will receive 34% of the profit. Finally, during the mature phase, in which operating margin is expected to be 40%, Alkermes' share of the profit will decrease to 18% while Amylin and Eli Lilly will each receive 41%. No guidance was given as to the expected timeframes for each commercialization phase.

ALLERGAN

David Pyott (CEO, Allergan, Irvine, CA)

Focusing mostly on Allergan's ophthalmology and aesthetics products during the presentation, CEO David Pyott only briefly touched on the LAP-BAND, the company's other obesity intervention products (the ORBERA and the EASYBAND), and Ozurdex, Allergan's potential treatment for diabetic macular edema (DME). During his review of each of Allergan's product areas, Pyott emphasized that the company is the "clear market leader" in gastric banding. As we understand it, Allergan believes the LAP-BAND has a peak potential revenue of between $500 million and $1 billion on an annual basis. However, revenue for the LAP-BAND is not yet back to its pre-recession rates, with a run rate of $20 million lower than in pre-recession times. Allergan has filed for lower BMI and adolescent obesity indications for the LAP-BAND, and expects to receive approval in 2011 and 2012, respectively; as a reminder, the company recently received a positive advisory committee review for expanding the indication to include lower BMI patients (for more information, see the December 7, 2010 Closer Look). The ORBERA is currently in clinical studies, and the EASYBAND obesity device is in the process of moving from feasibility studies to clinical studies. As for Ozurdex's potential for the treatment of DME, Allergan completed phase 3 enrollment in 2Q09, and expects to receive FDA approval for the indication in 2013, at the earliest.

AMGEN

Kevin Sharer, (CEO, Amgen, Thousand Oaks, CA)

As anticipated (because they rarely offer one), Amgen CEO Kevin Sharer did not provide an update on the status of the company's three diabetes drugs in development: AMG 151 (a phase 1 glucokinase activator licensed from Array BioPharma), AMG 221 (a phase 1 11B-HSD compound), and AMG 222 (a phase 2 DPP-4 inhibitor being developed in partnership with Servier). As a reminder, in April 2009 Amgen's EVP of Research and Development Dr. Roger Perlmutter stated that results from the phase 2 clinical trials of AMG 222 were on track to be released in 2Q09. However, we have not seen results for these trials as of yet, and it has been over one year beyond the anticipated date. During Q&A, we asked management one-on-one about the status of the three aforementioned compounds. While they did not disclose any new developments, they mentioned that the company will be releasing an updated pipeline soon, most likely in February. We have heard from a former Close Concerns associate now at a leading medical school alongside a former Amgen scientist that AMG 222 has been killed, though we note it is still on the pipeline on Amgen's website. It would be understandable if it is no longer in development as differentiation in this class has been hard to develop.

Questions and Answers

Q: Do you have any plans for succession?

A: Last year we named Bob Bradway as president, which the board takes seriously. Management continuity is very important to us.

Q: Do you have any updates on diabetes compounds in development? Rumor has it that you may have discontinued development of your DPP-4 inhibitor AMG 222.

A: We don't have any specific updates on these compounds at this point in time; we will be updating our pipeline on our website in the near future, around February or so.

AMYLIN

Daniel Bradbury (CEO, Amylin, San Diego, CA)

In front of a packed audience, Daniel Bradbury delivered a presentation on Amylin's strategic goals and recent developments. Bydureon, unsurprisingly, was a major topic of discussion, both in the prepared presentation and the following break out session. Overall, Bradbury expressed confidence that Bydureon would eventually gain regulatory approval in the US and the EU (where a decision by the EMA is expected in 1H11) and would become a "game-changing" drug given that its demonstrated efficacy, safety, tolerability, convenience, and Byetta heritage should appeal to patients, physicians, and payors. Audience members appeared most interested in the future regulatory path for Bydureon, and a few small updates were provided. Although specifics were undisclosed, Bradbury indicated that a protocol for the requested tQT study was submitted to the FDA recently and a response is expected sometime in 1Q11. It was inferred that the protocol stipulates supratherapeutic levels of exenatide to be achieved by means of exenatide infusions rather than Bydureon injection (positive because otherwise patients would be forced to experience levels that would prompt great nausea). Assuming a trial design is agreed upon this quarter, the company should remain on track to resubmit Bydureon to the FDA by the end of 2011. Despite communicating with the FDA, Amylin may still not be sure what prompted the FDA to request the tQT trial; this was not fully clarified in the session. Several exciting pipeline developments were highlighted: 1) phase 2 results for a once-monthly suspension formulation (reconstitution not necessary) of exenatide are expected in 1H11; 2) Takeda and Amylin continue to engage in phase 3 enabling activities for the pramlintide/metreleptin combination for the treatment of obesity (no timeline given); 3) phase 1 trials for the first candidate (AC167198), a type 2 diabetes therapy, to emerge from the company's partnership with Biocon will be initiated in 2011; 4) a sNDA was submitted to the FDA for the use of Byetta with basal insulins in December 2010; and 5) a rolling BLA including pre-clinical and clinical results for metreleptin in the treatment of type 2 diabetes and/or severe lipodystrophy in those with severe forms of lipodystrophy was submitted to the FDA in December 2010 (see December 20, 2010 Closer Look).

- **Bradbury expressed enthusiasm that Bydureon would eventually gain regulatory approval and would become a "game changing" drug.** He underscored the consistent, strong efficacy (both in terms of weight loss and A1c reduction), safety (low risk of severe hypoglycemia, potential reduction in CV events), tolerability (lower GI adverse events than Byetta), convenience (once-weekly dosing, no required dose adjustment), and extensive clinical experience with Byetta as major advantages of Bydureon that will drive prescriptions once approved. No mention was made of the need to reconstitute the drug and the current lack of a pen for Bydureon (Bydureon will be injected by a 25 gauge needle to start), limitations of Bydureon in our view. Bradbury appeared confident that payors would look favorably upon Bydureon giventhe demonstrated superiority of the drug to other commonly used anti-diabetic agents in the DURATION 1-5 studies and in the extensive claims data over the past five years for Byetta. Although pricing for this once weekly GLP-1 agonist is still unknown, many believe it likely that Bydureon will be priced at a premium to Byetta. Given this consideration, we view the results from the upcoming DURATION-6 trial that compares Bydureon to Novo Nordisk's liraglutide (Victoza) head-to-head as quite important. During the breakout session, Bradbury indicated that he believed Bydureon would be shown to provide superior glycemic control in the trial, and even if not superior in terms of A1c reductions, to him, Bydureon should still be considered superior based on convenience of use.
- **A few new updates were provided by Amylin regarding the upcoming tQT study for Bydureon requested in the last complete response letter from the FDA** (for more information, see October 20, 2010 Closer Look). Bradbury indicated that a protocol (which includes dosing through exenatide infusion rather than Bydureon injection) for the study was recently submitted to the agency and that a response was expected sometime in 1Q11. The company expects to also initiate the tQT study this quarter as well (editor's note - this has begun) as meet its previous guidance of resubmitting Bydureon to the FDA by the end of 2011. Surprisingly, it was revealed during the Q&A session that Amylin still does not exactly understand what prompted the FDA's request for this tQT study.

- **During the presentation, the company released the first details (to our knowledge) of a candidate to emerge from its partnership with Biocon to develop peptide hybrid molecules that combine the pharmacological effects of two separate hormones into a single molecular entity.** Named AC167198, the compound is under investigation for the treatment of type 2 diabetes and has shown the ability to lower blood glucose as effectively as exenatide but with much greater weight loss in animal models. No specifics were given on what two hormones comprise this compound, but we expect at least one of the hormones to come from one of Amylin's franchises (exenatide, metreleptin, pramlintide). Advantages of such a compound may include simplifying drug delivery (one injection instead of two) and streamlining the manufacturing process. Bradbury revealed that Amylin expects to file an IND with the FDA in the near future and expects to initiate phase 1 trials with the compound in 2011. For more information on this collaboration, please see September 15, 2009 Closer Look.
- **A brief review was given on the status of the pramlintide/metreleptin combination therapy under development with partner Takeda for the treatment of obesity.** Top- line results reported in February 2010 indicated that this combination treatment provided robust and sustained weight loss in overweight and obese patients while remaining generally well tolerated; nausea and injection site reactions were the most commonly reported adverse events. Based on these results, Amylin and Takeda decided to pursue phase 3 studies. During today's presentation, Bradbury indicated that the companies are still finishing enabling activities for the phase 3 trials which include: 1) scaling up manufacturing; 2) finalizing a trial dosing; 3) and finalizing a coformulation of metreleptin and pramlintide. As a reminder, Takeda will be responsible for conducting the phase 3 program for this drug combination, but Amylin will still be responsible for 20% of the costs needed to obtain approval in the US. Outside the US, Takeda will be responsible for all remaining development costs. No timeline was given as to when phase 3 studies may start.
- **Bradbury highlighted several recent developments with Byetta.** He indicated that Byetta is currently used by roughly 250,000 individuals with type 2 diabetes; since its launch in 2005, over 1.5 million individuals have used the drug. Notably, it was announced that three out ofthe top four Medicare payors have decided to include Byetta on their formularies in 2011, and Amylin hopes to gain approval with the fourth company (undisclosed) shortly. Finally, Bradbury highlighted the recent filing of a sNDA the FDA for the use of Byetta with basal insulins in December 2010 (see December 23, 2010 Closer Look) and the results from a retrospective claims data base study that found Byetta to be associated with lower CV risk than treatment with other anti-diabetic agents including insulins, TZDs, and sulfonylureas (see November 18, 2010 Closer Look). EXSCEL, the cardiovascular outcomes study for Bydureon, is expected to complete in 2016.
- **Bradbury elaborated on the plans of the company to expand the use of Symlin (amylin) in the United States.** In particular, Amylin hopes to gain market share in 2011 among individuals with type 2 diabetes on prandial insulin. The company will attempt to increase awareness of Symlin among individuals with type 2 diabetes and type 1 diabetes through collaboration on outreach efforts with the JDRF and will try to increase physician awareness of the compound through increased sales force visits to key physicians in the diabetes space.

Questions and Answers

Q: What's the status of your meeting with the FDA regarding the tQT study for Bydureon?

A: Our intention is to initiate the tQT study this quarter and to respond to the FDA by the end of this year. We're currently waiting for a response by the FDA on a final trial design.

Q: But you have submitted the protocol to the FDA?

A: Yes we have.

Q: Is there an ethical issue regarding the use of an infusion of exenatide or Bydureon in the tQT study?

A: In consultation with many - actually all - of the world's experts, the consensus is to use an infusion of exenatide to generate elevated levels of exenatide in the body.

Q: What level of supratherapeutic dose are you targeting?

A: We haven't given any specifics on this. As I mentioned, we're sill waiting to hear back from FDA on that and it would be premature for us to comment at this point.

Q: If you can use infusions of exenatide in the study, how much will that accelerate the time frame of conducting this study?

A: It's difficult for us to respond. We have not had the agency sign off on the design of the trial. I think we're sticking with our guidance at this time.

Q: Can you talk about your partnership with Takeda on obesity drugs in light of the challenging regulatory environment last year, and can you provide any more details on the financial arrangement of the deal?

A: We are very excited. We want to leverage physiological systems by using analogs of hormones. These analogs may be safer than the other obesity therapies that have been developed recently. We have seen a consistent safety profile with other analogs that we have tested, so we believe we are making an appropriate assessment here. Moving forward, we will be working on the co-formulation of metreleptin and pramlintide, scaling up manufacturing, and finalizing trial designs before commencing phase 3 studies.

In the deal with Takeda, we received $75 million in late 2009. There will be an 80/20 split in terms of expenses. That upfront payment would fund the work that would theoretically take us up to milestone payments that could be received through this deal. We haven't quantified those specifically yet. But we would expect milestones as we advance. There will also be tiered royalties that could reach double-digit percentage points. Takeda will take responsibility for all costs of the phase 3 program.

Q: Any intellectual properly challenges on exenatide or Bydureon?

A: We are very confident on our patent portfolio, but with Bydureon especially, we have an extra set of unique patents surrounding the delivery system used. We have 200 patents on exenatide and another 150 under review. So, we have very extensive patent coverage, especially with Bydureon.

Q: Can you comment on the current dynamics of the GLP-1 market? What impact due you expect on Byetta with the Bydureon delay?

A: Well, the uptake for any drug is different in the diabetes space. There is typically a longer uptake curve for injectable therapies than oral therapies. This is what we saw with GLP-1s. However, recently GLP-1s have been outgrowing the rest of the anti-diabetic classes. We are seeing new adoption among patients as well as new physicians prescribing the medication we didn't see in the ranks before. Advertising is helping both parties. The key for us will be to focus on new patients starts versus other therapies.

We did a market research study to see what physicians thought given what was going on with Bydureon. 96% agreed or strongly agreed that they thought Byetta was safe and effective. Most also told us that they would continue their patients on Byetta as long as they remained in control and did not see a reason to switch away from Byetta even though Bydureon was delayed.

Q: Can you talk about expectations for DURATION-6? How important to commercial potential will the outcomes be?

A: We remain confident that we can demonstrate superiority. But studies don't always pan out the way you expect, so there is a possibility that the comparator will be shown to be superior. But, we believe that even if we are not shown to be superior in terms of efficacy, Bydureon will still be the superior product given its convenience.

Q: I don't know if you gave financial guidance. Are you planning on cutting costs with Byetta sales down, or will you be a cash burner until Bydureon hits the market?

A: As we showed during the presentation, we expect to manage expenses consistent with our revenue. When Bydureon launch costs were excluded, we broke even in terms of operational cash flow in 2010.

Q: Will there be any more Bydureon launch costs?

A: There will still be prelaunch expenses, but given our planned response to FDA near the end of this year, we don't expect a lot of these expenses to occur in 2011.

Q: Why are you not concerned regarding the outcomes of the tQT study?

A: Well, we have done extensive work, and we have already conducted a tQT study with exenatide. But most importantly, there are a number of ways to analyze tQT studies, but one of the key variables is heart rate. When you use QTcI analysis, which is the most appropriate measure to use, we saw no effect with respect to Byetta with increasing concentration. Specifically, if you look at the effects of high concentrations, there is no effect on QT with Byetta.

However, a major reason why we are unworried is the DURATION-1 study. There were 66 patients (56 with mild, 10 with moderate renal impairment) and no impact on QT was observed in those patients.

Q: Where do the FDA's concerns come from? What was the study that concerned them?

A: We did not have clarification on what data. It is unclear what is driving this. That being said, we expect to continue our dialog with them. But we need to be pragmatic and address their concerns in the meantime.

Q: Did you ask them?

A: We typically don't tend to comment on our correspondence with the agency. But let us just say that it remains unclear to us.

ARENA

Jack Lief (CEO, Arena, San Diego, CA)

CEO of Arena Jack Lief began by reviewing data from the phase 3 program for lorcaserin and highlighting issues in the complete response letter that required additional non-clinical studies. Regarding the FDA's request to resolve the response relationship for lorcaserin-emergent mammary adenocarcinomas, Arena is planning to stick with its prolactin-mediated explanation; however, the company's still needs to finalize the protocol with the FDA. For more information on Arena's end-of- year meeting, see the December 23, 2010 Closer Look. *While Arena has previously indicated it would file lorcaserin in the EU before the end of 2011, during Q&A, Lief noted that the company first needs to address FDA's issues with rat tumors, providing no specific guidance for filing lorcaserin in Europe. In addition, in his prepared remarks, Lief also referenced the GPR119 candidate for type 2 diabetes, APD597. He noted that several patents have been filed and issued on GPCR technology and APD597 (including its use in combination with DPP-4 inhibitors). He characterized APD597 as "phase 2 ready" - as a reminder, Ortho-McNeil-Janssen terminated its partnership with Arena over this compound after the completion of phase 1 trials. Nevertheless, Lief explained that the phase 1 studies provided evidence for incretin stimulation (GLP-1, GIP, and PYY). We look forward to more information on these compounds.*

Questions and Answers

Q: Has the FDA defined how long you need to show increases in prolactin and how big the rise needs to be to be sufficient?

A: We're still in a process of going through the protocols. Regarding the work we had done previously on prolactin, we had some difficulty in showing a response. In the briefing document, we talked about a model where we saw a response. We believe we have an understanding of why we found it difficult to see the response and think it's related to stress, which can increase levels of prolactin. In terms of technicalities, I think we have a better understanding but it still needs to be finalized.

We do still need to send protocols of our study to the FDA. We just had the meeting a few weeks ago, so you can imagine we haven't had the official sign-off. We're confident we can show that prolactin is the actor

associated with these mammary masses that doesn't have any effect on humans. And we're confident we can show that to the FDA's satisfaction.

Q: The FDA made comments surrounding the modest efficacy. Assuming preclinical issues are cleared up, do you anticipate any problems around modest efficacy?

A: I don't. I think BLOOM-DM highlights how lorcaserin is important not only to obese population but also obese diabetics. An A1c reduction of 0.9% is important. Getting half of the out-of-control patients over the goal line was really excellent. Again, I think we need to discuss this with the agency but I think we meet all the guidance. Efficacy-wise, as a single agent, this is as good as it gets.

Q: Can you talk about your plans in the EU?

A: We are planning to file in the EU, but first need to address the FDA's issues with rat tumors. As soon as we've done that to our satisfaction, we'll file in Europe and elsewhere and move forward in that regard. EU is an important market but we are also targeting other important markets.

Q: What has been the response by investors to the company on its decision not to disclose the carcinogenicity findings?

A: I think some investors were surprised. I think other investors felt that because the FDA knew about this, they felt comfortable with that. We don't believe that the rat carcinogenicity studies were material and even in retrospect we don't believe they were material. There are many drugs with rat carcinogenicity findings in their labels. It's more of a labeling issue than an approvability issue. We just need to address the FDA's requests on prolactin and brain concentrations.

Q: Do you think the FDA and panel are on the same page?

A: My view is that the panel was a bit confused. There wasn't any pharmacologist or toxicologist. They couldn't really understand what was going on. A number of the panelists said they were confused - first they thought we had great explanations and then the FDA stood up and voted contrary to expectations.

The committee acknowledged they didn't have the expertise. They are data-driven and science-driven and clearly the conversations we're having are scientific conversations. In my mind the panel stated that they were unable to give an opinion on carcinogenicity data on animals because they lacked the expertise. Keep in mind also that the FDA is not a singular body.

Q: How do you plan to communicate these preclinical findings over the next 12 months?

A: We will communicate to investors as we progress towards re-filing or addressing FDA's issues. Certainly, we will make investors aware of material elements as we understand them. We have quarterly conference calls, we attend numerous investor meetings, and we do make presentations at medical meetings. ADA is in San Diego this year, so we'll be there with a number of presentations that have been submitted. So there will be a lot of news flow coming along this year, it's just a bit difficult to know how quickly that progress will be made.

Q: Can you talk about your cash runway?

A: We've previously guided that we expect to have $150 million at the beginning of this year. We will provide you with an exact number in the 4Q10 conference call, which is typically held at the end of February or early March. Certainly, $150 million is more than sufficient to get us through this year and next year. We'll give you an exact number in terms of spend in the 4Q10 call.

ARRAY BIOPHARMA, INC.

Robert Conway (CEO, Array BioPharma, Boulder, CO)

Array Biopharma, Inc. CEO Robert Conway announced to a full audience that the company had progressed its glucokinase activator ARRY-403 for the treatment of type 2 diabetes to phase 2 development. Acting on the liver and pancreas to lower and stabilize blood glucose levels after meals, the drug represents the

company's first foray into diabetes care. Partner Amgen will oversee the development process from phase 2 through commercialization.

ASTELLAS

Masafumi Nogimori (President and CEO, Astellas, Tokyo, Japan)

Astellas CEO Masafumi Nogimori emphasized the company's strategy to establish a competitive edge as a global category leader in five core areas: urology, transplantation, oncology, neuroscience, and diabetes complications/metabolic diseases. Urology and transplantation are currently Astellas' two strengths, and from the presentation, it seems like oncology will be the main additional focus moving forward. During Q&A, Nogimori provided an update on its SGLT2 inhibitor ASP1941 and reaffirmed Astellas' interest in diabetes complications. ASP1941 is currently in phase 3 in Japan, and in phase 2 elsewhere in the world. As we understand it, Astellas aims to launch ASP1941 in Japan by 2014 (assuming favorable regulatory review). Currently, all of Astellas' candidates for the treatment of diabetes complications remain either in phase 1 or preclinical studies.

Questions and Answers

Q: Can you provide us with an update of your activity in the diabetes and metabolic disorders space?

A: The most advanced candidate we have in this area is ASP1941, our SGLT2 inhibitor. ASP1941 is in phase 3 in Japan, and in phase 2 elsewhere. In general, since diabetes products require very large clinical studies, we are seeking potential partners for this compound. Ideally, we could find a partner prior to moving into phase 3 studies outside of Japan. Even though ASP1941 is our lead candidate in the diabetes and metabolic disorders space, our focus will be more on treatments for complications moving forward. Currently, all of our candidates for the treatment of diabetes complications are in still in phase 1 or are still preclinical.

ASTRAZENECA

Simon Lowth (CFO, AstraZeneca, London, UK)

Chief Financial Officer Simon Lowth presented on behalf of AstraZeneca, reviewing the company's pipeline and partnership strategies. Lowth emphasized that the company has put more focus on biologics in recent years and hopes to drive further into emerging markets as well as branded generics. There was no mention during the presentation of the company's diabetes compounds, which include recently filed SGLT2 inhibitor dapagliflozin, and the DPP-4 inhibitor Onglyza (saxagliptin) currently on the market.

BECTON DICKINSON

Edward Ludwig (CEO, Becton Dickinson, Franklin Lakes, NJ)

While CEO of Becton Dickinson Edward Ludwig spent the majority of his presentation speaking about BD's overall business and upcoming opportunities, he briefly highlighted the company's Diabetes Care business. Specifically, he characterized the Diabetes Care segment as a key "mid-term growth driver." In addition, he highlighted the company's commitment to innovate new pen needles in 2011 and referenced the recent partnership with JDRF, which he believes will leverage BD's expertise in insulin delivery and acute care infusion to launch new products to improve both the patient experience as well as outcomes for insulin pump users (for more information on this partnership, see January 19, 2010 Closer Look). During Q&A, Ludwig mentioned that the type 1 trends tend to be stable, whereas type 2 diabetes incidences and conversions to pen needles are "very positive" across the world. There were no other mentions of the Diabetes Care business in the prepared remarks or the subsequent breakout session; in particular, we look forward to hearing updates from the JDRF partnership, where BD is working on insulin delivery very broadly speaking as well as potentially other technology, as we understand it.

BIOCON

Kiran Mazumdar-Shaw (CEO, Biocon, Bangalore, India)

CEO of Biocon Kiran Mazumdar-Shaw presented a first look at the much anticipated phase 3 results for the company's prandial oral insulin IN-105 in India (data analysis is still ongoing). This "proof-of- concept" phase 3 study randomized 264 patients poorly controlled on metformin to either IN-105 or placebo (both arms were allowed to continue on metformin therapy; management provided no further information on enrollment criteria). The study did not meet the primary efficacy endpoint of achieving a placebo-adjusted A1c reduction of 0.7%; this is difficult to assess since the A1c reduction in the placebo arm was not disclosed. However, Mazumdar-Shaw attributed this to a higher-than-expected placebo effect, which she suggested could have been due to frequent SMBG testing (the average number of tests patients completed daily was not disclosed and we aren't sure if this was the same for both arms) - for example, large reductions in pre-meal glucose levels in the placebo arm were observed, which may indicate that behavioral modification could have confounded treatment effect (this "study effect" has been the bane of a number of diabetes trials and in our view should be expected - this is also difficult to assess since we don't know the magnitude of the placebo effect). The study did meet multiple secondary efficacy endpoints, including statistically significant reductions in postprandial glucose and a "significant drug effect in many subsets" (no information was provided on how these subsets of patients were characterized). While management did not elaborate on these specific subsets of patients, they noted that the A1c reductions were significant and "up to 0.8%" in the treated group (no further information was provided on these subpopulations). In addition, the study supported the safety of IN- 105 by showing no "clinically relevant" hypoglycemia (not defined), no serious adverse events, and no immunogenicity. Importantly, the drug was found to be weight-neutral, a significant advantage to all rapid acting insulins. We are curious how IN-105's efficacy compares to currently available prandial insulins. Management noted plans to initiate partnering discussions for IN-105 "very soon" and hope to conduct additional studies post-partnering. As a reminder, IN-105 is currently recruiting patients into a phase 1 trial under the US IND in type 1 diabetes patients (for more information on this trial, see October 22, 2010 Closer Look). In another pipeline update, management noted that Biocon's biosimilar insulin aspart and insulin lispro are scheduled to enter the Indian market in two years. Mazumdar- Shaw also clarified that Pfizer will join Biocon in India to exclusively co-market the company's biosimilar insulins in 2011. Finally, when asked about its partnership with Amylin, management said that they have a dual pharmacology peptide that targets glucose lowering and weight lowering; they urged listeners to go hear Amylin's presentation.

- **During Q&A, as expected, there was great interest in the Biocon/Pfizer partnership, especially with respect to the company's manufacturing capacity and commercial/ regulatory strategy.** While Mazumdar-Shaw could not disclose Biocon's current capacity, she noted that the company would be instituting a "multi-ton" capacity that will add "several tons" of capacity and would take roughly two years. [Editor's note: we are currently seeking to understand more directly how this relates to the number of units produced annually.] As for registering the biosimilar insulins in the US, Biocon remains in discussions with the FDA. While the company has had "good success" at arguing for biosimilar insulin in Europe (limiting the number of studies and defining the endpoints and populations), Biocon still needs to meet with the FDA to clarify what is required to submit recombinant human insulins and we assume US trials will be required. In general, management hopes that it will not have to conduct two large trials, but it remains uncertain whether the FDA will allow data from one large trial and whether the agency will accept Biocon's data from other regions of the world. We remain conservative on these fronts.
- **Mazumdar-Shaw estimated the global insulin market to be roughly $13 billion, and estimated that it would grow to $20 billion by 2020.** She also described the breakdown of global market share among major insulin players: 24% for recombinant human insulin, 23% Novolog (Novo Nordisk), 15% Humalog (Eli Lilly), 7% Levemir (Novo Nordisk), and 31% Lantus (sanofi-aventis). She noted that insulin represents 46% of the global diabetes drug market and is expected to grow 6% annually (factoring in the introduction of biosimilar insulins). In India, Biocon holds 10.8% share of the insulin vial segment and 13.2% share of the glargine vial segment (by volume). Our models suggest that the global insulin market will be over $15 billion in 2010; we won't know market growth until after the companies report 4Q10 and 2010 revenue but we would imagine overall growth would be above 6%. Biocon is expecting to roll out insulin pens in the second

half of 2011. Lastly, Mazumdar-Shaw estimated that the current market for biosimilar insulins is roughly $1.5 billion (we are curious how this market is split up among emerging markets). She cited projections that estimate the biosimilar insulin market will reach $5 billion by 2020.

Questions and Answers

Q: What is the relative importance of oral insulin versus going into a much larger volume market with the Pfizer opportunity? Where is the short-term growth coming from?

A: The oral insulin program is very important and we're very committed to it. It has the opportunity to be a game changer, so it is a very strong focus for us. It is now in a stage where we're ready to start looking for global partners. The data we've seen thus far is very encouraging and given us the proof of concept we were looking for. You will see a lot of activity here going forward.

Q: Why wasn't it wrapped up with the Pfizer deal to start with?

A: It is not part of the Pfizer deal. The Pfizer deal is only for biosimilar insulins.

Q: Can you talk about fermentation and the kilo capacity for your biosimilar insulin?

A: We have multi-ton capacity that we're putting in place. This is in addition to the capacity we already have.

Q: How much capacity do you have now?

A: We're not able to disclose this, but we're certainly putting in place several tons.

Q: How long will this take?

A: Two years.

Q: And will you have the FDA come and inspect your facility?

A: Yes. We have had FDA come before and inspect.

Q: Has the FDA shared guidelines with you for biosimilar insulins?

A: We are waiting for the US guidelines. As far as insulins, we are currently looking at the 505(b)(2) pathway.

Q: You mentioned lispro and aspart as part of your pipeline. When do you estimate those two candidates will be launched in any country?

A: In India?

Q: Yes, for example, in India?

A: A couple years away.

Q: Two years?

A: Yes.

Q: Before you signed the deal with Pfizer, how many other people were you negotiating with and how much demand was there?

A: There was quite a lot of demand from a few other major pharmaceutical companies and some generic companies. We went with Pfizer because we realized that biosimilar insulins are going to demand a large and intricate network and felt that Pfizer could address that for us.

Q: In Brazil, Biocon owns vial market share in regional tenders - how will the involvement of Pfizer in Brazil work?

A: For Brazil, we will approach it as a retail market.

Q: Insulin seems to be straightforward market - what will Pfizer bring to the table?

A: Insulin is not such a simple market, as one makes it out to be. There are devices involved, there are regulatory aspects - you must have good regional partners, which we did fairly well. Pfizer will only build on that. These are very very large markets and it would take a Pfizer to unlock them.

Q: In terms of having multiple insulins, I would suspect that if you have a lot of significant manufacturing changeover, that you and Pfizer would be best served by sticking to one biosimilar insulin.

A: We would perceive having a single insulin as a disadvantage.

Q: Where do you see your efficiencies, compared to the market leader?

A: In terms of tender markets, some years we win and some we don't. We did win the tender the year before. It's a fluctuating scene and it's hard to predict if we will win. In terms of pricing, we feel we are very competitive. In India, when we launched insulins about five to six years ago, we entered at a price point half that of Novo Nordisk and Eli Lilly, which were then forced to drop their prices by a factor of two.

Q: For pursuing the recombinant human insulins under the 505(b)(2) pathways, how many studies will be required and how many patients? How large will the clinical program need to be?

A: We are still in discussions with the FDA. We've had good success at arguing for biosimilar insulin in Europe, even within the biosimilar framework with limiting the number of studies and looking at endpoints and justifying the populations. I think our next step will be to go to the FDA to have a meeting with them to see exactly what's required. Enoxaparin, which is fairly complex, got approved with no clinical trials - in comparison, insulin is very well defined. That was under the 505(j)(2) though and this would be under the 505(b)(2). However, we don't expect to conduct two large trials. But we still don't know whether we need to do one large trial and whether data from the other parts of the world will work.

Q: Do you have any update on the partnership with Amylin?

A: We are working on dual pharmacology peptides that target glucose lowering and weight lowering. That's all we've disclosed so far, but I would encourage you to go to the Amylin presentation to hear more.

BIODEL

Errol de Souza (President and CEO, Biodel, Danbury, CT)

In an update on Biodel's activities, President and CEO Errol de Souza focused predominantly on its ultra-rapid-acting insulins (Linjeta, its follow-on formulations, and analog-based formulations), describing the lessons learned from the FDA's complete response letter, the company's next steps, and the company's partnership discussions. Notably, de Souza made it clear that Biodel will not be pursuing the original formulation of Linjeta, and instead will focus on its follow-on and analog-based formulations. He emphasized that the company has identified what was causing the injection site reactions, providing recent tolerability data to substantiate his claims. In addition, de Souza elaborated on the upcoming timeline for Biodel's ultra-rapid-acting insulin program. The company will select a follow-on candidate (and maybe one of the analog-based formulations) in 1Q11, complete human PK and tolerability proof-of-mechanism studies in 2Q11, and complete PK/PD proof-of-concept studies in 2H11. In 1H12, the company intends to initiate a phase 2 study (the company emphasized it is not taking any shortcuts), which should report in 2H12. As a reminder, Biodel also has a number of other diabetes products in its pipeline - an extended glargine, a glucose-sensing (smart) basal insulin, stabilized glucagon, and a sublingual insulin (VIAtab). These programs currently have limited funding (primarily for research), with partnering as the desired endpoint; de Souza stated that the ideal time to partner would be after phase 2 studies are completed. "Whether we do partnerships then or during or after phase 2 really depends on the economics so we can maximize the value to our shareholders," he said. As previously stated, Biodel has enough cash on hand to run operations until March 2012. From de Souza's remarks, it sounds like filing the new analog formulation would be in the ~2014 timeframe. De Souza also noted that the company could also pursue formulations that don't require refrigeration, and expand their horizons to emerging markets.

- **Ultra-rapid-acting insulins including Biodel's candidates could be a large improvement in insulin therapy.** According to de Souza, not much differentiates the three currently marketed prandial insulins (Novo Nordisk's Novolog, Eli Lilly's Humalog, and sanofi-aventis' Apidra) other than marketing and pen design. All have some lag time between injection and absorption into the bloodstream, which is the reason why their pharmacokinetic profiles in patients with diabetes do not match the natural insulin response to a meal. Regular human insulin has a TINS-50%-early of about 40 to 55 minutes, Novolog has one of 23 to 35 minutes, and Humalog has one of roughly 25 minutes. The delayed onset of action often leads to postprandial hyperglycemia, weight gain, and hypoglycemia. Ultra-rapid-acting insulins could have faster onset, fewer glucose excursions, and cause less weight gain. The TINS-50%-early of Linjeta has been documented to be between 8 and 18 minutes in clinical trials. Currently, at least three companies developing ultra-rapid-acting insulin products: Biodel, Novo Nordisk (NN1218), and Halozyme (PH20).
- **Biodel management said the company understands what caused injection site pain in the original formulation of Linjeta, and will aim to minimize injection site pain innew formulations in efforts to improve tolerability.** The excipient in Linjeta consisted of disodium EDTA and citric acid to destabilize hexamers of insulin; however, the disodium EDTA affected calcium levels, which led to pain further downstream. The newer formulations use calcium EDTA instead, which is said to reduce the amount of injection site pain. In a recent study, Biodel investigators assessed injection site pain using a visual analog scale (VAS), with zero representing no pain, and 100 representing significant pain. Linjeta averaged a score of 20.6, while the follow-on formulations BIOD-102 and BIOD-103 averaged much lower VAS scores- 4.0, and 9.0, respectively; for reference, Humalog users rate injection site pain to be approximately 5.0 on the 100-point VAS. As we understand it, Biodel is currently investigating at least four follow-on formulations (BIOD-102, BIOD-103, BIOD-104, and BIOD-105).
- **de Souza highlighted some of the lessons learned from the Complete Response Letter the company received in October.** For Linjeta, Biodel did not conduct any phase 2 studies, so for its phase 3 trials the company was asked to initiate Linjeta therapy at 50% of the normal insulin dose then titrate upwards. Poor titration at several centers ultimately affects some of the outcome analysis, thereby biasing the results against Linjeta. In addition, de Souza cited the use of recombinant human insulin as the active comparator as a major driver of slow recruitment, which created execution issues as sites were expanded beyond the US and Europe. Thus, Biodel now intends to conduct phase 2 studies next year before moving into pivotal studies again, and would ideally like to use Humalog as an active comparator (the company will need to run this by the FDA first).
- **As a reminder, Biodel also has a number of other diabetes products in its pipeline-extended insulin glargine, a glucose-sensing (smart) basal insulin, stabilized glucagon, and a sublingual insulin (VIAtab).** The extended glargine (sanofi-aventis' Lantus) product aims to extend the activity of the drug to make it a true 24-hour insulin and to suppress its peaks. de Souza noted that Lantus goes off patent in approximately three years or so, so now is the appropriate time to look into extended glargine. The glucose-sensing basal insulin is designed to combine Biodel's extended glargine with glucose oxidase, thereby causing more or less release of the insulin in response to the amount of glucose in the subcutaneous space. If this worked, it would represent a major technology advance; we don't have a good sense of all the constraints but we assume it would be quite complicated to achieve this. Regarding glucagon, Biodel intends to create a liquid formulation that could be used in pens and/or artificial pancreas systems. These programs currently all have limited funding (primarily for research), with partnering as the desired endpoint.

Questions and Answers

Q: I missed the presentation today. Did you make any material announcements? Any 8-Ks filed, or anything of that sort?

A: No. The only thing we announced last week was a reduction in our head count. In terms of strategy, I think we're better off taking new formulations that have taken care of the injection site tolerability issues. We'll select one or two candidates this quarter, go into the clinic next quarter for proof of mechanism and tolerability, and then move into proof-of-concept studies by the end of the year. We'll go into phase 2 studies next year.

Q: When do you plan to partner?

A: Our preference is that we have a partner that actually commercializes the drug. You need muscle to optimize commercial potential, which is what I've learned having been both on the Big Pharma and the biotech side. From my perspective, the ideal time to partner would be after phase 2 studies are completed. Once you start pivotal trials, you better have good alignment. From our standpoint, the milestones we hit this year should provide a lot of derisking from a PK/tolerability standpoint. Tolerability was a limitation earlier, and will be addressed in our first set of studies. At that point, we hope to start engaging the players. Whether we do partnerships then or during or after phase 2 really depends on the economics so we can maximize the value to our shareholders.

Q: Will your trial design for the eventual pivotal studies for the formulations you're investigating be the same as your prior studies?

A: I don't think so. We've learned quite a few lessons in terms of trial design based on our experience. One of the issues with our phase 3 trial design was that we did not conduct any phase 2 studies. Thus, patients in the Linjeta arm were started at 50% of the dose and titrated up. We hope to have that resolved with the phase 2 studies we conduct next year. In retrospect, if we didn't have to titrate up, the noise would have been minimized. Other things that are done quite often in phase 2 studies are to stabilize patients and then put them on three to six months of treatment to demonstrate non-inferiority for A1c. Of course, we would want agreement with the FDA. Trial design may end up being the same, or it may be very different. While non-inferiority seems straightforward, it is a tough hurdle. We want to make sure our drug is optimized for that endpoint, and we don't want to second-guess it.

Q: How will you prioritize between the type 1 and the type 2 study?

A: Our sense is that our preliminary studies and phase 2 studies will be done primarily in type 1 patients.

Q: Do you remember how many pages your CRL was? Seven or eight? Or 15?

A: It was in the usual range. You're in the right range. I wouldn't equate length with results though.

Q: What kind of CMC work would be required with the new formulation? Would it be intensive?

A: In terms of process scale up, it won't be a big deal - there will just be a few changes in protocol. Obviously, we'll have to do additional registration batches and foundation batches, which is all normal course. Wockhardt, one of our vendors, is under a warning letter (not related to Linjeta), but I'm sure that all of that will be well passed by the time we will need their services. In terms of our selection process, stability is very important. Obviously, we can't look at real-time stability, so as a surrogate we look at accelerated stability at 37 degrees and do our comparisons. The other part of the story that we are looking at is our plans with Linjeta. We stated earlier that we wanted to get it approved first then think about using it in pumps and the disposable pen we're working on. These were all going to come post-approval. Well, we're going to leverage all of the data there for the upcoming trials. We'll be looking at pump usage sooner rather than later, but we're not projecting any specific trials. We want to make sure to look at compatibility in the pump so the right kind of language in the labeling goes through.

Q: Can you talk a little bit more about your disposable pen?

A: At this time, it is premature for us to comment.

Q: You mentioned that in your phase 3 trials enrollment slowed by using regular insulin as a comparator, and that you'll be adopting a different strategy in the future. How will you do so in the regulatory pathway?

A: This is one of the questions we want the FDA to address. We will propose very clearly that we would like to do a study with Humalog as a comparator. We won't second-guess the agency, but it's an agreement we would like to get. It makes sense because Humalog is the proper active comparator to be used in this country. We've checked with two people who used to run part of the endocrine division at the FDA, and they said the agency should be amenable to this request.

Q: How did you end up submitting with recombinant human insulin as a comparator in the first place?

A: We submitted under the logical assumption that that was what the agency would require. Looking retrospectively, we realized that there was nothing that specifically said we had to do that. Consultants told us that we could probably use insulin lispro because it is the standard of care here, so it makes sense. We're not moving forward until we receive confirmation from the FDA that this is acceptable. It is one of the questions we will be asking the agency at our upcoming meeting.

Q: On your timeline, you will complete your phase 2 studies in the second half of 2012. Will you file after that?

A: Ideally, we would have a partner before we do pivotal trials.

Q: So you're looking at the 2013-2014 timeframe to file?

A: It would be premature for us to speculate that far ahead. It really depends on the number of patients we will need to enroll in our phase 3 studies, which will largely be determined by the phase 2 data. But you're probably in the right ballpark.

Q: If your product is successful, what are your thoughts about international opportunities?

A: It would be premature for us to speculate on that. It really depends what we end up pursuing. We're looking at several formulations and several presentations. What I mean by that is that the optimal formulation for the US, Europe, and many other countries may not be the ideal formulation in emerging countries. We could actually come up with formulations that don't require refrigeration, and expand our horizons to look at emerging markets.

Q: As a follow up comment, the reason I asked was because you'll need a source of insulin glargine for your extended glargine product. There are about five or six companies that make insulin glargine, but they're all outside of the US - in places like China, the Middle East, and Latin America. That's the reason why I asked.

BRISTOL-MYERS SQUIBB

Elliott Sigal (CSO, Bristol-Myers Squibb, New York, NY)

In major news, Chief Scientific Officer Elliott Sigal announced that the US and EU applications for the SGLT-2 inhibitor dapagliflozin have now been filed with the regulatory agencies. He noted that the drug satisfied the FDA's cardiovascular guidance and that the full integrated safety report will be made public this year. He emphasized the benefits of dapagliflozin: "moderate" consistent weight loss combined with blood pressure control and infrequent hypoglycemia. On the safety concerns, Sigal reiterated that the increase in external genital infections were mild-to-moderate and rarely led to discontinuations; similarly, the increase in lower urinary tract infections (UTI) were rare and the "majority" responded to initial treatment and there were few resulting discontinuations (for detailed coverage of a phase 3 monotherapy study published in Diabetes Care, see June 24, 2010 Closer Look). Finally, regarding the overall business, Sigal mentioned that the company has divested the non- pharmaceutical business to become a mid-sized pure play biopharmaceutical company.

CVS CAREMARK

Larry Merlo (President and COO, CVS Caremark, Woonsocket, RI) and Per Lofberg (Executive Vice President, CVS Caremark, Woonsocket, RI)

CVS, which merged with Caremark in 2007, is the largest pharmaceutical provider in the US and serves approximately five million Americans per day. While the CVS Caremark presentation did not directly mention diabetes or obesity, the company's president, Larry Merlo, focused on the expansion of MinuteClinic, a program of 550 clinics in the US that serve approximately 8 million patients annually through the provision of vaccinations, illness and injury exams, and wellness exams at fixed prices. The goals of MinuteClinic are to provide access, high quality, and low cost to a broad range of patients. Merlo also highlighted the program's necessity in our current political climate given the severe shortage of primary care physicians and growing population of insured patients resulting partly from the recent healthcare reform bill. Merlo stated that MinuteClinic will continue to expand in 2011 by adding more locations across the country. In the context of diabetes, the MinuteClinic website advertises that it provides "diabetes monitoring" care, which may include A1c, BMI, cholesterol, comprehensive foot, kidney function tests, and a review of lifestyle factors, all at a cost of $69- $114. The clinic offers to send these test results to a diabetes patient's primary care physician or specialist free of charge. This model of simple and convenient healthcare that MinuteClinic offers certainly brings into question the future role of the primary care physician in performing basic testing and analysis. Perhaps MinuteClinic is beginning a trend of basic care that can be performed well, affordably, and efficiently outside of a healthcare setting. On the other hand, in the case of an unexpected emergency at a MinuteClinic location, some patients may prefer the security of receiving care in a hospital or physician's office.

DEXCOM

Terry Gregg (CEO, Dexcom, San Diego, CA)

Dexcom CEO Terry Gregg shared the company's outlook on 2011, which the company is terming "the year of the patient" - throughout his talk, he emphasized the advantages of the Dexcom technology related to convenience, performance, and stability. Certainly these are the attributes that have prompted significant growth in 2010; in his talk, Gregg gave a preview of (better-than-expected) 4Q10 earnings, which included $13.6 million in product sales, more than double the $6.6 million from 4Q09. He also forecasted $67.5-$72.5 million in sales revenue in 2011, for ~70%-80% year-on-year growth. Notably, this is the first time the company has shared annual revenue expectations, a reflection of how the market has grown and become more predictable. Gregg also estimated for the first time penetration of type 1 patients using CGM at approximately 4%; this reinforced the potential in the category for us as there is certainly lots of room to grow. He estimated 2011 penetration for type 1 increasing to 7-8% by the end of this year and said that the reimbursement challenge had significantly declined although work still clearly needs to be done on raising awareness of both patients and HCPs. Gregg shared his thoughts on the company's many products in development as well, including the fourth-generation sensor and the fourth-generation /Animas integrated system (both already submitted for CE mark, with the US path forward to be clarified by the end of the month - this will be key information to come), the Insulet integrated system (where the generation of sensor to be integrated is still unknown but we would guess would be fourth-generation), the fifth-generation sensor (capable of transmission to hospital displays and smartphones alike), and the Edwards/Dexcom intravenous CGM for use in the ICU (facing developmental delays in the EU and regulatory uncertainty in the US).

- **Dexcom CEO Terry Gregg gave a preview of the company's 4Q10 revenue and an update on the multiple products moving through regulatory review.** Fourth-quarter product revenue totaled $13.6 million, a sequential increase of 26% from $10.8 million in 3Q10 and a 106% increase from $6.6 million in 4Q09. Annual product revenues exceeded $40 million, more than double over $18 million in 2009. 4,850 starter kits were sold in 4Q10 in a striking sequential increase of 24%, and sensor revenue grew 27% between 3Q10 and 4Q10. Gregg forecasted $67.5-$72.5 million of product revenue for fiscal year 2011 (i.e., 68% to 80%), and he noted that this figure does not include payments from Dexcom's partners. Management emphasized the need for the company to grow responsibly without straining its internal resources, which are already under pressure from growth so far: we understand that the company's back-office staff did not increase in size during 2010, although sales ramped from under $7 million in 1Q10 to $13.6 million in 4Q10.

This is testament to the impressive operating leverage we have seen at the company throughout its growth last year.

- **Gregg also gave details on the company's fourth-generation sensor, which will be offered as a standalone product and as part of an integrated pump/CGM in partnership with J&J Animas.** This is expected to be approved now late this year, following FDA delays announced in late 2010. We have the impression that both Dexcom and Animas are working very aggressively on this, which is very good news for patients; our research on pumps shows that combination products with CGM are very highly sought after by patients (this is the biggest request on pumps from patients aside from wanting smaller pumps - write Richard.wood@d-qa.com for more information). Gregg reminded the audience that the fourth-generation sensor will be 50% smaller by volume, more accurate due to new membrane technology (especially in the hypoglycemic range), and less susceptible to interference from the immune system. The fourth-generation product has been designed to be more scalable than the current sensor in terms of manufacturing space required, and it is expected to offer cost advantages over the current sensor as well. Notably, the fourth-generation sensor is already slated for use in closed-loop studies, of which Dexcom is involved in roughly a dozen worldwide. Dr. Ed Damiano (Boston U) intends to use the fourth-generation product in an upcoming project, and there is also a possibility that a French-government-sponsored trial will see the fourth-generation sensor used in conjunction with Debiotech's JewelPUMP.
- **Both the fourth-generation sensor and the integrated Dexcom/Animas product have been submitted for CE Mark approval, with European launch anticipated as early as the first half of 2011, prior to the expected US launch date.** Meanwhile, Dexcom will be meeting with the FDA this month to clarify the path forward for both the standalone and combined products. Management hopes to conduct clinical trials of the fourth-generation sensor in late 1Q11 or early 2Q11. The combined product could begin clinical trials immediately thereafter in mid-2011, and the combined product's PMA supplement will be filed after the standalone fourth-generation PMA supplement has been filed.
- **Insulet has been given responsibility to choose whether the companies' integrated system will use Dexcom's third- or fourth-generation sensor.** As a reminder, the integrated product was originally planned to integrate Dexcom's third-generation sensor with Insulet's first-generation OmniPod. However, when the FDA unexpectedly responded to the companies' submission with an eight-page request for multiple additional studies, it fell to Insulet to choose how the companies would go forward. As we understand it, the decision is between thecombination of Insulet's current pod and Dexcom's third-generation Dexcom sensor (the combination that was submitted) or Insulet's next-generation pod and the fourth-generation Dexcom sensor. One piece of learning from the conference was that Dexcom's third-generation sensor transmits at 402 megahertz, a frequency normally reserved for implantable medical devices and that the company's documentation to use this technology will expire in mid-2013, and though Dexcom has had luck with the FCC in the past, management is unwilling to speculate on the likelihood of renewal. As a reminder, one of Dexcom's goal at founding was to develop an implantable CGM; although we would like to see this developed, this is not a focus at present.
- **As we understand it, if the FCC's documentation is not renewed, Dexcom will lose the right to produce new third-generation sensors**, except to replace those of patients already using the product. Dexcom plans to have rolled out the fourth-generation sensor by mid- 2013, and so the FCC's decision is unlikely to affect the company's core business either way. Given this, from our view, Insulet's decision appears to rest more on which pod it would like to use rather than which sensor. While the "current" (larger) pod could be approved in a combination product sooner, we imagine Insulet would prefer to get all patients using a smaller pod as soon as possible following approval, and that on balance, this is likely relatively more important to the company than having an integrated pump/CGM sooner than Animas. From our view, we would imagine it would be challenging for the company to have more than one SKU for inventory purposes. As we understand

it, using the third-generation sensor together with a smaller pod is not an option for Insulet. Having a third-generation sensor as part of a combination product would also force an upgrade program both when a fourth-generation sensor was approved, as well as when a smaller pod was approved, although we imagine some patients would be willing to cover the cost of such upgrades. Of course, if Insulet moved ahead now to get the current pod and sensor approved in the combined product, Insulet would have to underwrite more new trials when the fourth-generation sensor was approved, which it is understandably reluctant to do. At this stage, we believe Insulet has committed to patients that the combination product will have its new smaller pod, and as such, we assume that Insulet's combination product will just come later than that made by Animas. While the current pod/third-generation sensor could probably be approved by late 2011, we assume that approval timelines for the "next-gen pod/CGM system" would be well into 2012. Still, we would imagine the companies would have significant demand for the next-gen separate pod and sensor separately from current users; it would remain to be seen without an integrated product (but with next-gen products) if Insulet could steal any share from competitors. Although Insulet said it was not counting on even being able to identify competitor pump users, we believe some will reach out when Insulet is offering its smaller pod - we intend to test these decisions in our market research in the coming few months.

- **Because Animas and Dexcom worked to develop the new transmitter** (see below) together, Animas has a period of six-month exclusivity following the launch of the Dexcom/Animas product. As we understand it, Dexcom management expects that the Animas exclusivity period will already have passed by the time the Dexcom/Insulet system reaches the market, which we assume is the case as well although we never bet on FDA timing anymore. (See our Insulet entry in this report for more on that company's next steps.) However it works out, the sensor-choice issue seems to be a major source of tension in a partnership that is already strained under the burdens of a demanding FDA.
- **Dexcom's fifth-generation sensor uses sensing technology adapted from the Dexcom/ Edwards intravenous CGM system, and Gregg noted that the sensor is being developed for "step-down" hospital units and is designed to be compatible with closed-loop systems.** Gregg showed data on the fifth-generation sensor's performance ina surgical ward: a nondiabetic patient who experienced stress hyperglycemia (~170 mg/dl) during surgery. The system tracked throughout the procedure, demonstrating resistance to the anesthesia, steroids and acetaminophen that the patient had taken. The sensor will be less accurate than the Dexcom/ Edwards product but more accurate than the company's other ambulatory sensors, as suggested by early human trials. (For details on the specifications of Dexcom's fourth- and fifth-generation sensors, see our full coverage of the Diabetes Technology Meeting in the December 31, 2010 Closer Look).
- **Interestingly, the fifth-generation product's "brains" will be housed in the transmitter rather than the receiver (as in previous Dexcom products).** This will enable integration with any sort of receiving device, whether pagers and monitors in hospitals (likely the initial market) or smartphones for consumer use. The integration of consumer and medical devices obviously represents a huge potential hurdle: FDA rules would treat the smartphone as a medical device as long as it serves as anything more than a passive display. For example, the iPhone is essentially a fancy display when it is coupled with the sanofi- aventis/AgaMatrix iBGStar, one way around this rule. Thus introducing a third piece of hardware that communicates with the sensor and plugs into the smartphone is one probable strategy for Dexcom. The downside of this approach is that it requires patients to keep the hardware attached to their phones all the time. It will be interesting to see how this issue evolves for Dexcom's fifth- gen and for medical monitoring in general. As we were reminded during our recent visit to the Digital Health Summit at the 2011 Consumer Electronics Show (see our January 8, 2011 Closer Look), the FDA appears too under resourced to develop regulations at anywhere near the pace of mobile health innovation. We don't know yet how the move to put the "brains" in the transmitter will affect the size of the transmitter although the footprint

sounds like it will be very similar; size seems to be perpetually an important question from a patient perspective.

- **As he has historically, Gregg characterized patients on multiple daily injections as a major focus for the company, and he appeared to strengthen this focus a bit in his JPM talk,** emphasizing, "Every patient on insulin is a candidate for CGM." Because patients are in such poor condition relative to "normal" A1cs, we believe that CGM can indeed help not only every patient on insulin but also every patient who does not have a normal A1c. In terms of driving increased awareness of CGM benefits broadly speaking, Gregg said that to date, benefits of CGM have been "pushed" to healthcare providers and patients but that the company is starting to see more "pull," i.e., patients requesting CGM from their doctors. This is being driven largely by online discussions on CGM. Interestingly, he also said that patient and provider commentary used to be more about the benefits of avoiding hypoglycemia by using CGM, but it is moving toward more discussions of better overall glycemic control, i.e., the benefits of avoiding hyperglycemia as well as hypoglycemia.
- **Gregg also said that pump integration would also help expand the market, but "pump salespeople want to sell pumps**." We believe once there are integrated products, this could have a major impact on pump and CGM penetration, since both new pumps will be perceived as better-generation products (Animas and Insulet) and in the case of Insulet, the smaller pump combined with a CGM is a big step forward. We also believe that since Insulet's pod will be substantially smaller, patients may be more open to an integrated product than they otherwise would be. We also believe the two integrated products will serve as greater competition for Medtronic's integrated product in the US; in the EU; internationally, Animas and Dexcom have an exclusive three-year commercial agreement, though the Veo's "low glucose suspend" feature will likely continue to represent differentiation for Medtronic. When asked about Medtronic's short-term CGM product, the iPro, Gregg also said that the goal of this technologywas "to drive pump sales." Despite this, in our view, we believe the iPro is very effective in showing type 2 patients the poor control that they are in; while they may have semi-acceptable or even acceptable A1cs, we believe seeing the glycemic variability after a blinded period can be a real wake-up call to both patients and providers and can prompt more active thinking about how to improve therapy.
- **When asked about the potential for type 2 patients to drive further growth in CGM,** Gregg said that this was happening to some extent. Specifically, there are now two coverage policies for type 2 patients. Cigna and BCBS Michigan, which offer positive (but very restrictive) reimbursement. That said, he said, there is no prospective data showing benefits of CGM for type 2 patients; he believes that there will be an investigator-initiated study coming out of Walter Reed showing a reduction in A1c, weight, and blood pressure coming from an investigator- initiated study. This will likely be shown at AACE or ADA in 2011.
- **On the marketing front for CGM**, social media is clearly important for Dexcom. Gregg spoke about the importance of viral marketing, of patients and providers sharing success stories about CGM, etc. He also emphasized familiarity with the Insulet and Animas salesforces, saying that approximately 15% had worked at MiniMed and did express that (in spite of the MDI commentary above) they would be effectively more "feet on the street" for Dexcom once the combination products were approved, which looks at this point like possibly 2011 for Animas/Dexcom and 2012 at the earliest for Insulet/Dexcom.
- **Gregg confirmed that the second (commercializable) generation of the Dexcom/ Edwards in-hospital CGM is now set for CE Mark submission (instead of wide European launch) in late 2011 - a delay announced on the previous day by Edwards CEO Michael Mussallem.** We understand that the US timeline is delayed as well, mainly for regulatory reasons. The FDA's requirements for glucose monitoring accuracy (including BGM) are in flux, and Dexcom management has said that they are holding off on clinical trials until the agency clarifies what it wants in terms of a submission. The original plan was to first seek approval of the "kludgy" (as characterized by Edwards management)-but- accurate first-generation product, as was

done in Europe, in order to enable real-world studies. However, if the FDA requirements are steep enough, Dexcom management would encourage Edwards to focus on submitting only the user-friendlier second-generation system.

- **Gregg noted that the reimbursement process for CGM is becoming easier, as evidenced by** the recent decision by some members of the Anthem consortium to reduce the proof required to show medical need. Physicians on these plans (as with other plans already) can simply run through a checklist rather than compiling and submitting patient documents. This is a big win as the time it takes for physicians to help patients start on CGM has been a drawback to date.

EDWARDSLIFESCIENCES

Michael Mussallem (Chairman and CEO, Edwards Lifesciences, Irvine, CA)

Edwards Chairman and CEO Michael Mussallem forecasted a solid year of revenue growth (6-8%) despite a 20% increase in R&D spending, roughly one sixth of which will go to critical care diagnostics. Although the majority of the presentation and Q&A session focused on Edwards' emerging transcatheter heart valve business (US launch anticipated in fall 2011 pending FDA approval), Mussallem referenced the Edwards/ Dexcom in-hospital continuous glucose monitoring (CGM) system during his prepared remarks. He noted that the European launch of the second-generation Edwards/Dexcom continuous glucose monitoring system has been delayed from late 2011 until 2012, with CE mark approval now targeted for the end of 2011. During the breakout session, Mussallem explained that the delay is due to the cumbersome and "kludgy" nature of the first-generation system (currently being tested post- approval in Europe). Mussallem said that Edwards is "working aggressively" to improve user- friendliness, and he noted that the first-generation system is already highly accurate and reliable.

Questions and Answers

Q: Could you comment on the delay in the European launch of the continuous glucose monitoring system?

A: We've been pursuing this. We feel like we've demonstrated that it's accurate and stable. Being able to get a sensor in the blood that will stay accurate over time is a big accomplishment. But it's still a little too kludgy. The start-up time, the number of steps - it's too cumbersome for broad adoption. We need to make it simpler to get it up and running in a hassle-free fashion. These are busy people, and giving them a great tool that's a hassle is not an advantage. We're working aggressively, and the goal is to have it CE marked by the end of the year for launch in 2012.

ELI LILLY

Dr. John Lechleiter (Chairman, President, and CEO, Eli Lilly and Company, Indianapolis, IN)

CEO John Lechleiter devoted a significant portion of his talk to a major partnership announced this morning between Eli Lilly and Boehringer Ingelheim to co-develop and co-commercialize several compounds for diabetes, including: BI's DPP-4 inhibitor linagliptin, BI's SGLT-2 inhibitor BI 10773, Lilly's novel basal analog LY2605541, and Lilly's LY2963016, an insulin glargine product that was publicly mentioned for the first time today. The overall theme of Dr. Lechleiter's talk was how Eli Lilly would successfully pass through what the company calls the "YZ Years" - a period of multiple key patent expiries that starts in late 2011. He cited the BI deal as an example of a mid-term strategy to maintain revenue even in the trough of the YZ years, and he noted that the intellectual property on the BI compounds will not expire until the late 2020s. Dr. Lechleiter closed his presentation with a list of important events that the company anticipates in 2011, including several related to diabetes. Potential regulatory actions include submission of Bydureon in the EU, approval of linagliptin for type 2 diabetes (submitted in 2010 in the US, the EU, and Japan), and FDA approval of Byetta in conjunction with basal insulin (submitted December 2010). Lilly also expects a resubmission of Bydureon based on the FDA's most recent complete response letter, the completion of the DURATION-6 trial comparing Bydureon to Novo Nordisk's Victoza, and the initiation of phase 3 trials for both Lilly's novel basal analog and its glargine product. The interest in diabetes continued through

the company's breakout session, where questioners asked about the BI deal, Bydureon, and whether Lilly plans to become a "one-stop shop" for managing groups of patients.

- **During a conference call to announce the news, Eli Lilly management laid out the terms of their "strategic alliance" with Boehringer Ingelheim.** Eli Lilly will pay BI €350 million (~$453 million) up front and as much as €625 million ($809 million) in success-based regulatory milestone payments for linagliptin and BI 10773. For its part, Lilly may receive up to$650 million in success-based regulatory payments on its basal insulin analogs. Additionally, BI can opt in to an anti-TGF beta therapy for renal fibrosis, granting Lilly up to $525 in opt-in and success-based regulatory milestone payments. The two companies will share equally in ongoingand future development expenses, commercialization expenses, and gross margin. If and when a compound does well on the market, the originating company will also receive performance payments from its partner.
- **Linagliptin showed comparable efficacy to Januvia (Merck's sitagliptin) and Onglyza (BMS/AZ's saxagliptin), the DPP-4 inhibitors currently available in the US, in its seven completed phase 3 trials.** However, Januvia and Onglyza are excreted primarily through the kidneys and thus require dose adjustment in patients with moderate to severe renal insufficiency. Because linagliptin is mainly excreted unchanged through the enterohepatic system (only ~5% of excretion is renal), BI's drug requires no dose adjustment due to kidney disease - the main area of differentiation cited by the companies. According to CDC estimates based on NHANES data from 1999 to 2004, the prevalence of moderate to severe CKD in people with diabetes is roughly 9.2%. Still, it remains to be seen how much these patients, their providers, and their providers value taking the full dose of an unfamiliar DPP-4 inhibitor rather than a reduced dose of a drug that is already on the formulary. Doctor education will be key. Introducing another DPP-4 inhibitor to the general type 2 population will presumably be a tough sell, and thus far BMS/AZ have not made the task look at all easy, although we would not underestimate Lilly and BI's potential on this front, particularly because we believe this class has lots of room left to grow.
- **Linagliptin was submitted for regulatory review in the US, Europe, and Japan in the second half of 2011.** Thus far BI has applied for linagliptin to be indicated as monotherapy and as an add-on to TZDs, metformin, sulfonylureas, and metformin and sulfonylureas together. Submission of a fixed-dose combination with metformin (fast-acting) is slated for 2011 in the US and EU and 2014 in Japan, while no timeline has been set for planned fixed-dose combinations with pioglitazone and extended-release metformin. (As a reminder, the FDA approved BMS/AZ's saxagliptin/metformin XR combination Kombiglyze XR this November. Earlier this week, Merck announced that the agency had accepted an NDA for an extended release version of Janumet, its sitagliptin/metformin product.)
- **The SGLT-2 inhibitor BI 10773 began phase 3 testing in mid-2010, and its six trials are set to enroll roughly 10,000 patients.** In a phase 2 trial of 408 patients with type 2 diabetes, BI 10773 caused statistically significant placebo-adjusted improvements in A1c (~0.6- 0.7%) and body weight (~4.5 lbs). Most notably, the frequency of urinary tract infection was low (<1.5%) and balanced among all groups, while the incidence of genital infection was also low (~1% in the BI 01773 group compared to no infections with metformin or placebo). Given that urinary tract and genital infections remain the biggest area of concern around the class, a clean profile in this regard would be a valuable point of differentiation for BI 10773. (With a launch projected for 2014, BI 10773 will likely come to market after BMS/AZ's dapagliflozin, which has now been filed, and J&J's canagliflozin [slated for simultaneous US/EU regulatory submission during 2012].) However, as Lilly management noted on the call, it remains too early to characterize BI 10773's safety or efficacy.
- **Eli Lilly's novel basal analog LY2605541 has been shown in phase 1 trials to possess a flat and long-lasting steady-state action profile, low within-patient variability, and an "acceptable" safety profile -** the most common adverse event was hypoglycemia. Two phase 2 trials began in early 2010 and are expected to report in Q211, the phase 3 program is set to begin in the second half of this year, and regulatory submission has been targeted for 2014. Eli Lilly has been

slower to enter the basal insulin area compared to sanofi-aventis (Lantus [insulin glargine]) and Novo Nordisk (Levemir [insulin detemir]). Novo Nordisk also plans to launch Degludec and DegludecPlus (fixed ratio combination of Degludec and NovoLog) in 2013, raisingthe bar for LY2605541 yet higher (especially given that Degludec has demonstrated potential for thrice-weekly dosage). Besides less-often-than-daily dosing, competitive qualities of a new basal analog include very low hypoglycemia, affordability, and miscibility with GLP-1. Hopefully phase 2 results later this year will offer insights into how LY2605541 matches these and other key criteria. Notably, we've heard of other insulins in develop as well that have less frequent dosing; one we discussed yesterday is bypassing the FDA and developing in Russia.

- **Eli Lilly also revealed that it is developing an insulin glargine product called LY2963016.** Phase 3 studies are planned to begin this year so that regulatory submission can occur in 2014. Management was reluctant to classify the basal analog as a "biosimilar" or "bio- better," saying that these terminological issues remain to be decided by regulatory agencies. They gave little reason to think that the molecule is effectively different from Lantus. Instead, in the JP Morgan breakout session, management noted that they plan to be competitive through pricing, manufacturing capabilities and "diabetes know-how," and by launching the analog with their "latest delivery device" - a topic on which they declined to elaborate. Also in the breakout session, management suggested that although "there would be significant opportunity everywhere," Lilly sees emerging markets (such as China, where the company recently announced a new Shanghai research facility) as especially compatible with the glargine product. We are unsure whether they will be manufacturing there, but this has been a key advantage for Novo Nordisk to date.
- **BI also has a chance to opt in to LY2382770, Eli Lilly's anti-TGF beta antibody under study for kidney disease.** The antibody selectively inhibits TGF-beta 1 isoform, which in preclinical studies has been seen to contribute to renal fibrosis. Renal fibrosis characterizes a late stage of many kidney diseases, including diabetic nephropathy. Lilly is currently enrolling 400 patients with CKD and type 1 or type 2 diabetes for a yearlong phase 2 trial with once-monthly dosing of LY2382770, which is scheduled to complete in December 2013 (Clinical Trials ID: NCT01113801). Pending successful completion of phase 2, BI will be able to exercise its up-to-$525 million chance to opt in to future development and commercialization.

Questions and Answers

Q: Do you see these types of transactions - that is, two companies with late-stage compounds - do you see more of these opportunities in the future in the industry, as everyone is challenged for resources and trying to maximize efficiency?

A: I think this is a great agreement for Eli Lilly and Boehringer Ingelheim. It's an opportunity for one plus one to make three, literally. Boehringer Ingelheim is a company we have had a lot of experience working with (e.g., on Cymbalta) - our company cultures are compatible, so things like governance and daily operations are going to be easier because of the track record we've had together. Of course, in these types of partnerships, we have to find the right products and the right fit, and I think we have done so in this partnership, as it offers us two nearer-term launches and validates the potential that our basal insulin offers. It will give us an opportunity to do better with Eli Lilly products - including Humalog, Byetta, and Bydureon (when that gets approved).

It's a really exciting time for us. We believe that we are creating one of the most robust pipelines in the industry when it comes to diabetes. We now have with this agreement two oral agents - SGLT2 and DPP- 4 inhibitors - that have the potential to be best in class. Linagliptin is currently under regulatory review in the US, Europe, and Japan, while phase 3 studies have been started with the SGLT2 inhibitor. Our basal insulin analog is currently in two phase 2 trials and will be entering assessments shortly. If those phase 2 trials are successful, we expect to start phase 3 trials later this year, with the potential for submission in 2014. We're also developing another basal insulin analog - a new insulin glargine product - and we're very excited about it. We expect to start phase 3 trials later this year. This partnership is very exciting, and is an incredible

opportunity for us to have a significant diabetes presence. I believe that it not only benefits medicines in this alliance, but also our currently marketed products.

Q: Will the basal insulin glargine product be a bio-better? Or a biosimilar?

A: Because of the evolving regulatory landscape, that designation would be provided by regulatory authorities in different countries. What we can say is that we believe that we would be able to offer it at a competitive price, as we have the diabetes know-how and the manufacturing capabilities. In addition to bio-betters, innovation can come in a number of different ways. We clearly have a lot of expertise on delivery devices (for which we also have a pipeline), and we intend to launch our insulin glargine product with the latest delivery device.

Q: Where do you see the most opportunity for your insulin glargine product? In the US? In emerging markets?

A: There would be a significant opportunity everywhere. I do believe the opportunity in emerging markets is very significant. The insulin market in China right now is $400 million, and it is expected to increase tenfold in five to seven years. We are making significant investments in China now.

We have also recently expanded our research capabilities in China, with a facility in Shanghai. We are tapping into huge Asian populations with diabetes, which may or may not have similarities to populations in the West. It is a long-term commitment, and we are bolstering our research capabilities.

Q: What are the challenges of launching in a primary care type setting, being third to the market with an asset like that [linagliptin]?

A In a certain way we have been there before with Cialis and Cymbalta. We will make sure the product is properly positioned so that we can have a value proposition to physicians. We believe linagliptin can offer that. We acknowledge that payors are increasingly becoming the gatekeepers, but we feel confident that we can be successful at launch. Down the road, we have plans for fixed-dose combinations of linagliptin with metformin, as well as with pioglitazone. As far as having an SGLT2 inhibitor - there are only two enterprises that have both a DPP-4 inhibitor and a SGLT2 inhibitor in their portfolios, so we'll have the opportunity to combine those as well.

Q: Would the fixed-dose combination with metformin be extended release, or would that be for a subsequent submission?

A: Initially it would be BID, then what you suggest as a follow-on.

Q: How are you thinking about pricing in Europe on a go-forward basis?

A: I think we all hope that some of the measures that were taken quite suddenly in 2010 were an aberration. In the aftershocks of the economic downturn, we've been watching some areas. I don't necessarily think there will be low-digit annual declines in prices over an extended period of time. I think it would be premature to rubber stamp 2010 on to 2011 or 2012. I think it's going to be important for us to be careful and thoughtful about our value proposition. In Europe, there is a different degree of penetration in generics in different countries - low penetration in Spain and Italy, and greater penetration in Germany.

Q: Back to the future question about disease management. With the Boehringer Ingelheim products, and diabetes medications that are generic, you could theoretically be a one-stop shop. Do you think five years from now you will protect populations instead of selling insulin and pills?

A: It could be. We basically have the broadest portfolio in the industry, which gives us a number of advantages. I think we can study these products in various combinations, not just as products, but as solutions to patients. The extension of that is to look further down the road, and engage in more creative solutions, especially for payors.

Q: Do you see yourself in a position to capitalize if it happens, or do you want to try to make it happen?

A: We have to see how the market develops. Accountable care organizations are increasing, but so far the ramp-up has been slow. We expect those kinds of organizations to increase and expand to manage the overall increasing healthcare costs we have seen. At this stage I don't have the ability to comment more, but certainly a number of doors and options open with the portfolio we have. We could become the premier diabetes company in the world.

Q: How are you looking to position your GLP-1 products and the DPP-4 and SGLT2 inhibitors? From a resourcing standpoint - take Januvia for Merck as an example - you have finite resources in diabetes. Are you looking to expand? How will you prioritize your products?

A: Having a broad portfolio would allow us to have enormous efficiency. We don't intend to duplicate everything. Rather, we just want to make sure we are trying to manage efficiently. We will have to scale up to make sure we do justice to the opportunity we believe we have. With a number of potential upcoming launches - of linagliptin, potentially Bydureon, and two basal insulins - it's truly an exciting time in terms of what we think we can do in terms of positioning. In terms of positioning DPP-4 inhibitors, we can get as elegant as we want, but it's customers who are making the choices, and there is still an injection barrier today. We view both DPP-4 inhibitors and GLP-1s as significant growth classes. In the case of the oral DPP-4 inhibitors, they are likely to be used earlier in therapy. We also see significant growth in the GLP-1 class. Bydureon when it's approved will be a significant catalyst. (Note - this answer is incomplete - we didn't catch all the details.)

Q: What are the data that led to the FDA's QTc concern on Bydureon?

A: It's difficult for me to comment and speculate as to whey they made that decision. It's not an issue they highlighted in their first complete response letter. We are engaged with the authorities, and as we've shared we will comment more when we have the tQT study protocol approved. I believe we're on track to resubmit by 2011.

Q: You haven't had a meeting?

A: We won't comment on our regulatory communications.

ERESEARCH TECHNOLOGY

Joel Morganroth (CEO, eResearch Technology, Philadelphia, PA)

eResearch Technology (ERT) is a cardiac and respiratory services provider that helps centralize and efficiently manage clinical trial data. One of the company's main areas of focus is on cardiac safety services (including standard ECGs, arrhythmia monitoring, thorough ECGs). While diabetes was not specifically mentioned during the presentation or breakout session, ERT has recently been promoting its Cardiac Safety Solutions as a potential tool for pre-approval cardiovascular safety studies for type 2 diabetes drugs. With this in mind, we assume they'll be busy for years to come.

EVOTEC

Werner Lanthaler (CEO, Evotec, Hamburg, Germany)

Evotec CEO Werner Lanthaler emphasized drug discovery as the company's core competency, highlighting the company's work in the diabetes arena and its beta cell regeneration program. Lanthaler asserted that the company is "clearly the leader of beta cell regeneration technologies at this stage" and has "big strategic engagement in this area." He emphasized that no one has done more comprehensive screening for beta cell regeneration factors than Evotec. In order to build more alliances in the next few quarters, the company is considering granting other companies access to their screening results. No updates were provided on Evotec's EVT770 program itself, as management declined to comment on the specific molecule and targets in the program during the lightly attended Q&A session. As a reminder, Evotec has had a growing presence in the diabetes arena in recent years, having engaged in partnerships with Andromeda/Teva (DiaPep 277), Boehringer Ingelheim (a novel insulin sensitizer), and most recently, MedImmune (EVT770) (please see December 23, 2010 Closer Look). Evotec intends to deliver data from the phase 3 data on DiaPep 277 in the next 12 to 18 months.

Questions and Answers

Q: Can you elaborate on your EVT770 beta cell regeneration program - on the specific molecule and its targets?

A: We're not disclosing any information at this time. All we can say is that we have internally validated the molecule and its targets.

FOREST LABORATORIES

Francis Perier, Jr. (CFO and SVP of Finance, Forest Laboratories, New York, NY)

After covering Forest Laboratories' "Late Eight" candidates in development, CFO and SVP of Finance Francis Perier provided an update on its phase 1 and phase 2 programs, including TTP399, the lead glucokinase activator (GKA) in its GKA program licensed from TransTech Pharma in June 2010. Perier noted that early phase 1 testing suggested that the pharmacological enhancement of GKA activity lowers blood glucose in patients with diabetes. Forest Laboratories will be initiating its phase 2 program for TTP399 in 1H11. As a reminder, under the terms of the partnership Forest is responsible for development and commercialization costs, with global rights excluding the Middle East and North Africa (see June 18, 2010 Closer Look*).*

GLAXOSMITHKLINE

David Redfern (Chief Strategy Officer, GlaxoSmithKline, Middlesex, UK)

David Redfern provided few diabetes-related updates during GlaxoSmithKline's (GSK) presentation at this year's J.P. Morgan conference. He indicated that despite the recent regulatory decisions on Avandia, the onset of generic competition for Valtrex in the US, and the favorable growth of Pandemic (flu vaccine) sales in comparison to 3Q09, the company still achieved strong underlying growth in 3Q10 at a rate of 5% (although, as reported in the October 22, 2010 Closer Look, drops in Avandia franchise sales accounted for a 2% swing in total company sales from 3Q09). Management has noted that they expect sales from this franchise to be minimal from 2011 onward and that additional losses beyond those expected with sales returns and inventory losses may be incurred in the form of legal expenses. As a reminder, on September 23, 2010, the EMA suspended sales of this once blockbuster drug, and the FDA voted to restrict sales to type 2 diabetes patients who cannot control their blood glucose with other medications. In regards to its pipeline, Redfern said that GSK has not yet decided on when it will begin announcing results from its albiglutide phase 3 program, which was initiated in February 2009 and contains eight clinical trials. GSK expects to receive results from several of these trials internally in 2011, and to the best of our understanding, anticipates launching the compound in the US several years from now. No updates were provided on the development of anti-CD3 therapy for the treatment of type 1 diabetes. Results from the phase 3 DEFEND-1 trial are expected in 2Q11.

Questions and Answers

Q: For albiglutide, when can we expect phase 3 data?

A: GSK has not completely determined that internally. We will publish the data when we are ready to do so.

Q: I believe some studies should have completed now for albiglutide given that the program started in 2009.

A: It's a three-year program. So we will be receiving data over the next two years. How this data will be communicated will be decided internally, but we will have internal data this year.

HALOZYME

Greg Frost (CEO, Halozyme, San Diego, CA)

Halozyme CEO Greg Frost announced several new updates for Halozyme's Ultrafast Insulin program this afternoon, which seeks to develop a best-in-class prandial insulin product through the coinjection of the company's synthetic human hyaluronidase PH20 (rHuPH20) with currently marketed insulin products.

First, he indicated that the two ongoing phase 2 trials (NCT01194258 [type 2 diabetes], NCT01194245 [type 1 diabetes]) comparing insulin aspart (Novo Nordisk's Novolog) plus PH20 and insulin lispro (Eli Lilly's Humalog) plus PH20 to insulin lispro alone just completed enrollment earlier this month at 110 participants each. Results will be announced sometime in 2012. Second, it was revealed for the first time that Halozyme had initiated a phase 1 insulin pump study using PH20 (NCT01275131). The goal of the study will be to compare the pharmacokinetic and glucodynamic properties of insulin glulisine (sanofi-aventis's Apidra) plus PH20 and insulin aspart plus PH20 with each insulin alone when infused continuously though an insulin pump over a three-day period. Most interesting to us will be whether the pharmacokinetics and glucodynamics (i.e. Tmax, GIRmax, etc.) of the combination therapy remain consistent over the three-day span when the exact same area of skin is subjected to the hyaluronate-degrading effect of PH20. Data from this trial is expected to be available in 3Q11. In our view, positive results from this trial have exciting implications for the artificial pancreas (many believe current insulin analogs are not rapid enough to develop a fully closed-loop system) and should, along with results from the two phase 2 studies, drive partnership discussions. During the breakout session, Halozyme management indicated that they were exploring all partnership opportunities including those with major insulin companies, small insulin companies, and insulin pump companies.

- **Halozyme's synthetic human hyaluronidase PH20 (rHuPH20) acts locally and transiently to depolymerize subcutaneous hyaluronate, creating nanochannels in the interstitial membrane that facilitate the diffusion and spread of therapeutics into the bloodstream when injected under the skin.** The goal of Halozyme's Ultrafast Insulin program is to develop a best-in-class, rapid-acting insulin by coinjecting PH20 with an insulin product. Halozyme believes that such a therapy will result in a more consistent, morerapidly absorbed, and faster-acting insulin product, which reduces the risks for postprandial hyperglycemia, hypoglycemia, blood glucose variability, and weight gain. Promising results have been achieved in the six phase 1 or phase 2 trials carried out thus far, with demonstrated improvements in insulin action, absorption, the number of hyperglycemic excursions, rates of hypoglycemia, and percent achieving targeted glycemic control when human insulin, insulin aspart (Novo Nordisk's Novolog), insulin lispro (Eli Lilly's Humalog), or insulin glulisine (sanofi- aventis's Apidra) were co-administered with PH20 in individuals with type 1 and type 2 diabetes.
- **Halozyme is currently conducting two additional phase 2 clinical trials for PH20 used in combination with currently marketed rapid-acting insulin analogs.** Both trials are identical except that one will be conducted with individuals with type 1 diabetes while the other will be conducted with individuals with type 2 diabetes. The trials will compare three- times-daily injections of insulin lispro plus PH20, insulin aspart plus PH20, and insulin lispro alone over a 12-week span in regards to glycemic control efficacy and safety (rates of hypoglycemia). Frost announced during the presentation that both trials recently completed enrollment in January 2011 (n=110) and that results will be announced in 2012.

Questions and Answers

Q: What's the difference between what you and MannKind are trying to accomplish?

A: Their focus is to prove that their inhaled insulin product is as good as existing alternatives that are injectable. Our perspective is different. We feel we need to demonstrate best in class and achieve differentiation over existing products via postprandial hyperglycemia, hypoglycemia, glucose variability, and A1c reductions. It's hard to tell whether we can get all of these, some of them may be more mutually exclusive. For instance, if you target a reduction of hypoglycemia, if might be harder to control hyperglycemia and vice versa. Still, the studies are well powered to detect differences at the hypoglycemia and hyperglycemia ends. If we can get both that would be great.

Q: How well is your stuff working? How come sanofi, Eli Lilly, and Novo Nordisk aren't knocking down the door to get their hands on this product?

A: Well, the bottom line is that you are going to have to ask them. There may be some reasons though. For the incumbents that have big market shares (i.e. Eli Lilly and Novo Nordisk), for them to partner with us, they would gain a competitive edge for their existing franchise. However, for this gain, they will have to pay a fee. They may look at that as a net neutral. One question of the industry is how long each of those insulin franchises will last when biosimilars become available. We just don't know. They may have a different view. For sanofi-aventis, Apidra is quite a small player and they focus on Lantus.

What we can say, however, is that when the phase 2 studies and the pump study wrap up, I believe that there will be no additional data that we will need for partnership discussions. Going through this work with pumps, looking at different insulin coformulations, what we're really doing is providing ourselves with more options down the road so that we have a better chance of getting what we want. The pump market is a small but very important piece of the pie.

Q: If the pump study is successful, will pump companies possibly become your customers or just insulin companies?

A: There is an orthogonal approach in pump use itself. The pumping community represents the thin edge of a wedge. They are generally highly motivated and a very important community, but a relatively small community nonetheless. If we get into the community first and get these individuals to adopt our product, we will certainly see a trickle down effect into the rest of the insulin using diabetes community. All options are on the table. We are looking at the incumbent insulin companies, smaller insulin companies, and pump companies. Our priority foremost is to get the data, then to make a decision from there. But the pump data will help complete the mosaic.

Q: What does the pump study help us understand?

A: If you have a continuous infusion at a single site, every time you get a bolus, you can see whether you get the same acceleration of insulin action that we see with injections throughout the entirety of the three to four days the pump is used. We want to know whether the insulin will perform consistently over this entire period or if there is some change. We believe that we'll see that there really isn't any change in action.

HUMAN GENOME SCIENCES

H. Thomas Watkins (President and CEO, Human Genome Sciences, Rockville, MD)

In H. Thomas Watkins' presentation for Human Genome Sciences, almost all of the focus was directed toward the Lupus treatment Benlysta: the pending approval, future commercialization plans, and future research efforts into additional indications. The company expects Benlysta to be a major driver of growth both in the near and long term, with multi-billion dollar revenues by 2015. In a recent FDA advisory committee meeting, the committee voted 13-2 to approve the drug; the PDUFA date for Benlysta is on March 10, 2011. Watkins also briefly reviewed albiglutide (formerly Syncria), a novel GLP-1 agonist created by Human Genome Sciences that is comprised of a modified human GLP-1 peptide fused to human albumin. Because of the extended half-life that the human albumin and GLP-1 modifications confer (four-to-seven days), once-weekly or less frequent dosing is possible. In 2004, Human Genome Sciences out-licensed the product to GlaxoSmithKline for upfront and milestone payments that could amount to $183 million. Human Genome Sciences also stands to receive royalties from worldwide sales at a single digit percentage rate. Thus far, Human Genome Sciences has received $33 million from GlaxoSmithKline. GlaxoSmithKline initiated the phase 3 program for albiglutide in February 2009, and Watkins noted that there are eight phase 3 trials currently underway. However, because GlaxoSmithKline is in charge of the phase 3 program, Watkins was unable to provide any updates as to when results from any of these trials may be seen. From a search of clinicaltrials.gov, it appears that the two phase 3 trials closest to completion (albiglutide vs. liraglutide [NCT01128894] and albiglutide plus insulin glargine vs. insulin glargine plus insulin lispro [NCT00976391]) are expected to complete in September 2011. To our best knowledge, pending positive results from the phase 3 program, approval in the US may come as early as 2013-2014.

Questions and Answers

Q: Can we expect to see albiglutide phase 3 data this year?

A: This is a GSK development program. It is their development program. I refer this question to them. There are eight ongoing trials. They have different populations and sample sizes in the trials. From what we have heard, enrollment in the trials was occurring in a prompt fashion. However, all data and interim look discussions will have to take place with GSK.

HUMANA

Michael McCallister (CEO, Humana, Louisville, Kentucky)

Humana CEO Michael McCallister reported that, in an effort to improve healthy behaviors and habits, 65% of the company's spending is on patients' social characteristics and behavioral patterns. McCallister also expressed sensitivity to the high price of diabetes care, and he explained with great excitement that the company distributes diabetes supplies in-house to all of its patients in an effort increase patient familiarity and to allow patients to save money on outside sources. In the breakout session, we asked about measures that were being taken by Humana do educate its patients about obesity and type 2 diabetes prevention in light of the company's interest in behavior change, wellness, and diabetes care. At length, McCallister explained the company's devotion to preventative care and the challenges that come with attempting to change unhealthy behaviors and promote weight loss and wellness. In an effort to overcome these challenges, McCallister explained that the company is conducting a worksite wellness program with its employees. He suggested that many different methodologies such as financial incentives could be used in an effort to promote positive behavior change and prevent obesity.

INSULET

Duane DeSisto (CEO, Insulet, Bedford, MA)

Insulet CEO Duane DeSisto gave a thorough overview of the company's OmniPod patch pump and a vision for where the company is headed in the coming year. He reviewed the specs of the next- generation pod (one-third smaller, 25% lighter) and also reaffirmed Insulet's plan to complete a clinical trial in 1Q11 to position the product for an FDA approval before the end of 2011. Notably, he mentioned that it "seems likely" that no clinical trial will be required for the new smaller pod in the EU, however, in which case Insulet would launch the next-generation pod there in 2011. DeSisto also shared that Insulet now has 25,000 users; about 500-700 of them are overseas and 30% are under 18. On the financial front, he briefly reviewed financials, noting that in December Insulet paid off its $60 million Deerfield Partners credit line nine months early, saving $5 million, and he warned potential competitors about the high barriers to entry in the patch pump market (e.g., regulation, manufacturing, differentiation). In the breakout session afterwards, DeSisto and CFO Brian Roberts elaborated on the company's yearlong plan to switch its users onto the new pods and PDM. In response to a question about the Insulet/Dexcom integrated pump/CGM product, DeSisto gave insight on the company's upcoming decision about which generation of Dexcom sensor the system should include. The third-gen CGM will be subject to an "issue" with the FCC in 2013 when the documentation for its current frequency expires, whereas the fourth-gen CGM is part of Dexcom's arrangement with Animas (for additional details, see our entry on Dexcom above). While getting approval for a combo product with the smaller pod and fourth-generation sensor would clearly take longer for Insulet than the combination system already submitted, we imagine it may make sense to go for the more advanced system so that all patients ultimately use the smaller pod, inventory is easier to manage, there is only one pod SKU, etc. We look forward to hearing more about a decision on this front.

- **DeSisto gave an update on the regulatory status of the next-generation OmniPod.** As a reminder, the new design is one third smaller and 25% lighter than the old pod, with the same 80-hour life and 200-unit reservoir. Human factor studies are nearly complete, and Insulet has submitted a clinical trial design and timeline for FDA review. The proposed trial would enroll 100 patients across three centers, commencing in the first quarter of the year and lasting for 45-60 days total (since not all patients would begin the 30-day study period at the same time). Submission is targeted for 2Q11; DeSisto said he anticipates approval by the end of the year although we are not altogether confident about this since the FDA has been so disappointing in its progress in 2010. Meanwhile in Europe, as we understand it, the EMA has so far been suggesting that the next-

generation OmniPod is a repackaging rather than a new product and thus would not require clinical trials. DeSisto said that if the agency maintains this perspective following its in-person meeting with Insulet (and the new pod) in February, the next-generation OmniPod could "unequivocally" launch in Europe in 2011.

- **Thus far, Ypsomed has launched the OmniPod in several European countries, including Germany, the UK, The Netherlands, Norway, France, Sweden, and Switzerland and it sounds like progress is quite good to date.** DeSisto reminded the audience that Ypsomed is a descendant of Disetronic and understands pumps, reimbursement, and "where the pumpers are" - to be sure, Ypsomed is a powerhouse in the EU and is starting out with a major advantage Insulet didn't have in the US when it launched - significant brand awareness. Australia is the next targeted market, with a launch in China sought by the end of 2011. DeSisto explained that regulatory approval in China takes roughly two years and that Insulet began the process roughly one year ago. So far, 500-700 people have begun using the OmniPod in the UK and Germany since it was launched over five months ago. DeSisto also noted that Insulet's US business grew slowly at first; he said that Ypsomed's minimum quantity requirements were non-material in 2010 and would be "pretty non-material" in 2011. As a reminder, to maintain its exclusive rights to the OmniPod in these markets, Ypsomed must make yearly minimum purchases from Insulet. Over the companies' five-year agreement, these minimum purchases total $100 million - though DeSisto said he thinks both companies would be "dramatically disappointed" if sales were not higher than this. As we understand it, the partnership ROI is very positive for Insulet- one mid-level Insulet employee manages regulation in Ypsomed markets, and another is responsible for labeling in those territories and these are the only costs associated with the program outside of the royalty to Ypsomed.
- **The OmniPod is currently worn by 25,000 patients - about 2% of the US type 1 population (1.4 million patients) and approximately 7% of the insulin pump market (350,000 patients, 25% of the overall type 1 population).** He showed estimates that the US type 1 population will grow to 1.7 million by 2018, with the penetration of those patients who pump increasing to 50%. Meanwhile the European type 1 market [1.1 million patients] has 12% penetration, and China's type 1 market [1.2 million patients] has penetration far below 5%. DeSisto praised Insulet's 52-person sales force for the progress they've made during their two years in the field. He believes they are the most productive salespeople in the arena, with productivity rising from 2009 to 2010.
- **DeSisto shared demographic data on Insulet's current users.** Of Insulet users, 30% are children under 18 (Insulet's fastest-growing segment) and 60% are under 40 years of age. The company estimates the lifetime value of each customer to be at least $20,000; DeSisto noted that the attrition rate has settled back at 9% after rising to 10-11% in 2010. He said that the two leading causes of attrition are medical problems (usually unrelated to the pump itself) and financial trouble, with 30-to-40-year olds being the most likely patients to quit. Meanwhile, the attrition rate for those under 18 is only 4%, which DeSisto sees as understandable: "If my child went on this product, I'd probably go without food as long as I could to make sure the pod stayed on them."
- **DeSisto reviewed the barriers to entry in the patch pump market, including regulatory hurdles (especially given the new class 2b medical device classification that requires a clinical trial), manufacturing challenges, and OmniPod's simple design.** He observed that in 2010 Insulet produced four million pods at high standards of safety and accuracy ("we believe it's the safest pump in the marketplace"). Quipping that "cost is everything," he told the audience that the new pod's low cost of goods will enable gross margins of 65% or more (up from 50% on the current pod and $5 and below-per-pod margins in thecompany's early days). He also said that other companies "can't make it simpler" than the OmniPod and that the next-generation pod represents a defense against potential competition based on size.
- **Noting that managed care organizations look mainly for reduced costs and improved outcomes, DeSisto reviewed data suggesting clinical benefits of the OmniPod.** In a

yearlong retrospective study, 59 patients (47 MDI, 12 pumpers) were followed after they began using the OmniPod. The MDI patients achieved a mean A1c decrease of 0.49% from a mean baseline of 8.26%, a statistically significant change (Kane et al., Infusystems USA, 2010). DeSisto also said that many pump patients find themselves using less insulin after switching to the OmniPod. He cited evidence that conventional pumps may err in basal insulin delivery by 25% due to hydrostatic effects when long tubing is used (Zisser et al., J Diabetes Sci Technol 2010). Additionally, he noted that a half-hour interruption of basal insulin infusion (due to infusion site disconnection) has been linked to blood glucose increases of 1 mg/dl/min (Zisser, Diabetes Care 2008).

Questions and Answers

Q: There's so much interest around your pipeline and the FDA challenges around all companies in diabetes. People are focused probably too much on timing, but could you give an update on your thoughts about the next-generation pod and what happens over the next few months with regard to clinical studies and submission?

A: Where we are is pretty simple. Since our last (earnings) call, we submitted a protocol, but there's a new requirement for cleaning blood glucose meters and removing errant blood. We had to resubmit based on this; we had a conversation with them, and they said they'd get back to us in January. In the interim, we've completed human factor studies. The reports aren't written but we're pretty much done.

We've chosen three clinical sites for the trials. We chose sites that had A) access to pump patients and B) an IRB that meets no less than every other week, since we don't know when the FDA will say "go." We're recruiting patients, targeting - in a perfect world we'd start in the last week of January or the start of February. The trial puts us to the end of the quarter, and we'd write the report hopefully in early Q2. I've never found this written anywhere, but they seem to try to get back to you in 90 days with questions; hopefully they get back to you in 30. Any guidance we give will not include the next product. It's a potential upside, but we don't control it.

Q: You've said that the new pod will influence gross margin. How do you think it will influence the top line?

A: Every salesperson and everyone on the management team knows someone waiting for our next- generation product. I think a whole subset of people knows it's coming and wants to wait. We've not clearly articulated how we'd switch out current patients, because we don't want to get everyone excited - let's say it takes the FDA two years to approve, for example. We've learned from our early stages, when demand was gated by our manufacturing capacity. The last thing in the world I want to do is answering those types of phone calls. We know there's pent-up demand, but we're not giving guidance outside the company as to when the new pods will be available. On the regulatory piece, for the CE mark, we talked to the EMA, which we think was the right approach. They deem it as a repackaging of an existing product, and they seem to have no idea why we need a clinical trial. They want to look at the product in the first week of February. If this holds, we will file submission for the CE mark, which would dramatically accelerate launch in Europe. Where are we in the ability to produce? We have a full-blown line up in China. We want to have products being manufactured for human use by 1Q11. One line of the new product could produce at maximum 500,000 units per month. It would be earmarked for 300-350,000 units of the new product per month, then we want a second line, and then a third. After that, we would sunset the old pod. If we've done that math, it feels like we're shooting for January 2013 to have the old pod donated to the Smithsonian as a brilliant idea.

Q: It's not like people are spending $4,000 up front; I'm interested in the idea that patients are waiting for a product that's one-third smaller and somewhat lighter. Do you believe that people are waiting?

A: Absolutely there's pent-up demand. For example, I saw a parent with a little kid who was six months old - the pod looked like a second head. The next step down is amazing: one third smaller and 25% lighter.

Q: When the switchover happens, you'll just start sending people next-generation pods?

A: We haven't gone through all the details. You need a new PDM (personal diabetes manager) for the next-generation pod, so it will be a formal, organized switchover. Obviously people coming up for renewal would be first, as would vocal customers (laughs). We need to be methodical; we really need to make sure production is in place so there are no interruptions.

Q: Will you in the 4Q call articulate a swap-out plan or a market-conversion plan? What is the impact that's going to have in terms of inventory and your gross margin over that period of time?

A: You will see us swap out cash for inventory - the pods have a two year shelf-life - in the back half of the year based on where we are in the regulatory process and manufacturing. We have to swap out people's handhelds. So you won't see that uptake in margin in the first quarter, because it will be offset by the PDMs. The ROI for the new product is, I think, two-to-three months.

Q: Do you expect that process of changeover to last only one quarter?

A: It will be over the course of a year. You learn something new when you produce 300,000 pods instead of 100,000. We'll accelerate production with the second line, and the third line will let us sunset the first-generation pod. It's a six-to-twelve month timeframe.

Q: Can you talk about the pricing of the pod and the PDM?

A: We have a very different model than for other insulin pumps; it's much more pay-as-you-go. This is how we got access to managed care a few years ago. Under the old model, there are upfront costs of roughly $6,000 and $160 a month for infusion sets, etc. Now it's $600 up front - roughly one-tenth the initial cost - and $280 per month assuming ten pods per month. When you run this out, around a four- year timeframe we become more expensive. This was good because most insurance plans have four-year terms, and at the end of year five it flops. Also, the average person stays on a plan for an average of 2.5 years and then either you change jobs or change plans. Our model is a way to defer costs; it helped companies get very quickly over the curve.

Q: During your presentation you talked about how you work with Ypsomed on the European market. Maybe for those of us not as familiar, could you explain that relationship in more detail?

A: Our relationship with Ypsomed is a five-year deal, giving them exclusive rights in 11 countries if they meet minimum annual purchase requirements. We produce the products in the appropriate languages and are responsible for maintaining CE mark (we wanted to set that up ourselves in case the partnership goes sideways). They are responsible for clinical work, education, and reimbursement. The launch schedule is all around reimbursement, not approval. First were Germany and the UK, two of the bigger markets. They've also launched in Scandinavia, and France just got on board. Australia will be next, and hopefully China by the end of the year. The deal has been good for us - Ypsomed knows everyone in Germany, while we'd spend millions just finding out who to talk to. It allows us to open markets, get exposure to KOLs. It's a low-cost - in fact, a profitable - way to get our toes in.

Q: What's the pricing in Europe?

A: It's pretty comparable. The UK has some limitations, with three or four tiers of payment. The higher tiers are closer to the US and the lower tiers are not. We get to sit on the sidelines and get educated.

Q: Would you talk about the integration of the pod with continuous glucose monitoring? Where are you today?

A: Our primary focus in on the next-gen pod. In conjunction with Dexcom, we submitted the old pod with their third generation sensor. We got back an eight-page paper that finished by saying "don't consider this all inclusive, strong language to follow." They wanted us to do insulin stability, animal testing. We said, "We're already on 20,000 mammals - you can't get any better than that!" We got the impression that anything put through in 510(k) under the prior administration was considered suspect. All the scrutiny with BGM, pumps - everyone is suspect. Our old product, in order to get approval, would have required all the testing we'd just done for the next-generation pod. We told Dexcom we're just using a new platform; it makes no sense to

spend all that money on the old product and not take advantage of the new one. As soon as we get the new pod's submission in, we need to turn to the CGM integration. But the good news is that the engineering is not that complicated. Our question is what sensor do we use: gen three, gen four, they're working on gen five. For us it's pretty simple. Gen three has FCC issues coming in 2013. Dexcom believes they can fix this and get going; if they can fix that and get going then we're good. But I need more than a six-to-twelve-month timeline for this new product, so we need to get to the bottom of that. Gen four has obligations with J&J Animas in the US and internationally, and we need to make sure we understand these. I think that not having the product for the next 24 months doesn't impact my business negatively. But we want to have it; we really want to have it. Everything is built off getting the next-generation pod approved. We've talked to the EMA about it, and they think this piece is not a big piece. The hope is that the regulatory process, now that the second-generation pod will have been approved by the current regimen in Washington, will be different.

Q: Is there a technical barrier to having open architecture for Dexcom's gen three and gen four?

A: Our understanding is that the technology is different. The frequency used by the gen three is expiring. There's new hardware and new ideas for gen four. Whatever gen five may be, they are all different, and we need to know how to communicate (between pod and sensor).

Q: With the Ypsomed partnership, is that $100 million minimum revenue to you?

A: Yes. As we sell to them, they pay.

Q: Is the chance that the FDA requires more than you're contemplating - I know you can't say zero, but would you put it at "exceedingly remote?"

A: We are over-communicating to ensure we hopefully have to do this only once. Having said all that, they could decide to change their mind. I understand where they're going and what they're trying to accomplish. Still, this is a repackaging of a product that is already on 25,000 patients, with arguably a very good safety record. Our manufacturing facilities were just inspected with no citations.

Q: What are the obstacles that prevent the OmniPod from taking 15% market share?

A: Frequency and reach. We are continuing to drive awareness. We have people in Massachusetts, in our backyard, who have never seen of us, never heard of us, who come into the lobby and want to find out what's going on. Would I start increasing the sales force? Absolutely. In Texas, one of our best reps gets all of their business from just three centers: there are huge opportunities. Given that we want to sunset the old products and that the new one maxes out at 500,000 per month, I'm running out of capacity in a heartbeat if I double the sales force right now. Also, we want to get operating cash flow to break even and then go positive. To pick up that 10% margin, it would be great to sell fungus if it meant - as good as you people have been to us - never needing to see you again. We're trying to take advantage of what we're seeing. No other patch-style pumps are on the horizon in the next 12-24 months and clearly there won't be one that's easier to use. We don't want to make the misstep of selling more than we can produce and run into problems with the next-generation. But the opportunity to go wherever we want is there. We are looking for 1.4 million people in a country of 300 million, and you can't do that overnight. Growth in this market takes time; it's not Facebook.

Q: I've heard talk that a newer test, I think called GlycoMark, is being used in Japan and Europe. Have you seen that used in any studies here?

A: Only in one, and it was recent. People are starting to look at that and at glycemic variability. A lot of this is being spun out of closed-loop studies; it's coming from physicians who have participated. We can argue about if and when the closed loop will ever come, but a greater understanding of diabetes has come from these studies. The gold standard for most of these guys is still pretty much A1c.

Q: What have you learned from your sales force about current pumpers' interest in the next-generation system. 75% of your user base has been MDI patients, but it now sounds like it's more like 70%. I think the new pod might be much more attractive to current pumpers, and less susceptible to criticism by your competitor's sales force - they call it "the tumor," which is pretty nasty.

Q: Part of that question is really: what does the next-generation have on ability to grab Medtronic users? The majority of growth for the company has come from patients not on pumps previously, but this may be an opportunity for the product to move the market over.

A: When people on the market are looking for a new pump and see our product, we're doing very well. But some people are signing up for a new pump before they are even on the market. So now I'm looking for 250,000 people - an even smaller number to find. We are doing paid searches. When people search online about diabetes our ads appear, to make it easier for patients to find us. We've shown the next- generation pod to existing pumpers who were kind of staunch; you could tell they were surprised at how small it could be. Our big competitor has all these patients' names, addresses, and emails, but we are getting there. It's said that every person with diabetes knows six others with diabetes. If you multiply our install base by six, that's starting to become a big number. Still, we have to execute. Could we shoot ourselves in the foot? Yeah, we could - the question is how quick we could recover. I think the big challenge is to go from 0 to 600,000 (pods manufactured per month); I think Charlie (Liamos, newly announced COO) is a great addition to the team.

Q: If someone interviewed 100 random diabetologists, how many are huge advocates, lukewarm, and negative? And how important are they?

A: Very important. That said, a person who has diabetes and wants our product will change doctors, run through broken glass, and do whatever they can to get it. We've seen it happen. I think if you survey 100 diabetologists on the East Coast, 60% know our company, like the product. 30% say a pump is a pump, and 10% say I haven't heard of these guys. Probably on the West Coast, flip it all around because we haven't been there as long.

Q: What percentage of patients do those 60% of physicians have on pods?

A: If you look at the major diabetes centers in the East, with the exception of a couple that are staunchly Medtronic, we're getting at least half of patients if not more.

INTARCIA THERAPEUTICS

Kurt Graves (Executive Chairman, Intarcia Therapeutics, Hayward, CA)

Executive Chairman Kurt Graves provided several updates on Intarcia's lead product, ITCA650, which delivers a continuous infusion of exenatide through the FDA-approved DUROS device. He also listed three ambitious goals for 2011: 1) secure a partner for ITCA650 in the first half of 2011 (a partnering process is currently ongoing); 2) prepare for an end-of-phase 2 meeting with the FDA next week (1/17 - 1/21) and to initiate a phase 3 program for ITCA650 in type 2 diabetes in 1H11; and 3) strengthen the organization towards the second half of 2011 (human resources, financial, platform/pipeline) and consider the possibility of completing an IPO in 2H11. Certainly, the company has many milestones in 2011 and we look forward to hearing more on this device. According to Graves, there is strong IP around ITCA650, including 345 patents that will protect the use of the device through 2027. He also emphasized several advantages of ITCA650, including the guaranteed 100% compliance (which is expected to be a major positive for reimbursement) and potential improvements in nausea and efficacy (which must be borne out in phase 3 studies). He closed the presentation by discussing the market potential of ITCA650, focusing on a four-month commercial assessment by a "worldwide market research firm" (we believe this was a leading consulting firm although we cannot confirm it) that valued the product as a multi-billion dollar opportunity. While we believe nearly any diabetes compound can be characterized as such given the number of people with diabetes, from our view, the major questions on this compound relate to IP and tolerability. Intarcia hopes to reach the market between 2014 and 2015.

- **Intarcia has two primary technology platforms: 1) technology that stabilizes proteins and peptides at high temperatures for up to two years; and 2) a small osmotic mini-pump that enables transforming a twice-daily injectable medication (Amylin's Byetta) into a once or twice per year implantation procedure.** Graves briefly referenced phase 2 data of ITCA650, highlighting the comparable (potentially slightly superior) A1c reduction - please see our coverage of these data from Dr. Robert Henry's presentation in our final EASD report, sent

out in the December 31, 2010 Closer Look. Dr. Henry also characterized the implantation procedure as 10 minutes (as opposed to five minutes, suggested by Grave). Nevertheless, Dr. Henry noted that the device can be installed by a doctor, physician assistant, or nurse practitioner. Finally, he suggested that the ITCA650 60 g/day dose has been selected for phase 3 trials.

- **Graves reviewed the device insertion process.** The device is inserted directly above the belt line, after the patient is given shot of a local anesthetic (such as lidocaine). The physician must pierce the skin to make a 5 mm insertion point, after which he/she uses a tool to slip the DUROS device under the skin (with a bandage to cover the insertion cut; no stitches). Grave estimated that physicians will make, on average, $250 per procedure for every patient.
- **Graves elaborated on the proposed phase 3 program for ITCA650.** Since the company plans to position ITCA650 as a second-line therapy after metformin, it plans to conduct a phase 3 superiority study comparing ITCA650 against Merck's Januvia and Takeda's Actos (with metformin as background therapy). The primary endpoint will be A1c reduction and thesecondary endpoint will be a composite of A1c reduction and weight loss. Intarcia hopes to show improved GI tolerability as well as the long-term benefits of compliance. Given that both the DUROS device and exenatide are FDA-approved, ITCA650 will go through the 505(b)(2) regulatory pathway. Finally, Graves noted that the COGS are "very low" and that the company will consider several possibilities for expansion after the initial launch, including geographical expansion, collecting disease modification data, and applying for other indications - he was specifically interesting in showing ITCA650's potential to prevent or delay the onset of type 2 diabetes, based on the current understanding of how GLP-1 therapies may protect beta cell function.

Questions and Answers:

Q: Who manufactures the device?

A: We acquired the device from Alza and have exclusive worldwide rights to the device for ITCA650.

INTUITY

Emory Anderson (CEO, Intuity, Sunnyvale, CA)

Intuity CEO Emory Anderson reviewed the attributes and advantages of the company's POGO All-in- One blood glucose monitoring system, which integrates test strips, lancets, and meter into a single unit. Anderson revealed that as part of the 501(k) process, a clinical trial is currently being conducted in three US locations (with 50 patients in each trial). Efficacy will be assessed according to the ISO standard 15197:2003 as for other blood glucose meters. Progress seems to have been slowed slightly by the FDA's new manufacturer requirements for the prevention of pathogen transmission from sharing BGMs. Apparently, the requirement that every patient use a separate device has forced Intuity to manufacture more devices than it otherwise would have at this stage of development. Pending 510(k) approval, the company intends to conduct a low-cost "targeted launch" to validate its business model, in which the company's sales reps will target high-prescribing endocrinologists and other physicians who treat insulin-using type 1 and type 2 patients. Anderson noted that upon approval, Medicare reimbursement would be immediately accessible through existing BGM HCPCS codes for all-in-one devices as well as test strips/reagent and lancets. Anderson also said that several major private insurance companies view the device positively based on initial research supporting the possibility of improved adherence with POGO. Also of interest, he seemed confident about the device's prospects for shelf space with major retailers. We aren't sure whether this would relate to a store brand, or getting on major formularies. On the manufacturing front, Anderson did not shed light on pending or completed agreements. We assume manufacturing will take place offshore - still, this meter will be more expensive than traditional meters and at least initially, the focus on Medicare makes sense given the valuable code for all-in-one BGM devices that Abbott got for Sof-Tact in ~2001.

IPSEN

Stephane Thiroloix (Executive Vice President, Ipsen, Paris, France)

During Ipsen's presentation, Stephane Thiroloix provided several new details on Roche's ongoing decision regarding the future fate of Roche/Ipsen's once weekly GLP-1 agonist taspoglutide. As a reminder, dosing was suspended in all ongoing phase 3 trials for taspoglutide this past September because of higher-than-expected trial dropout rates related to tolerability issues (primarily GI-related) and elevated rates of hypersensitivity reactions (please see September 10, 2010 Closer Look). Since then,Roche management has communicated that the company has been investigating the root cause of the hypersensitivity reactions observed with the drug (with impurities being one hypothesis) and exploring the option of using different formulations to mitigate the elevated rates of GI-related adverse events. While Thiroloix explicitly stated that Ipsen had not yet received word on the decision from Roche, he indicated that Roche was investigating a number of different hypotheses including the presence of impurities, issues regarding the manufacturing process, the pH of the compound, and the peak concentration the drug generates. Also interesting was Thiroloix's comments on the possible decisions that Roche could make. First, he stated that if issues were found with taspoglutide itself, all development would be stopped, suggesting to us that Roche may only choose to pursue further development if the issue is thought solvable and isolated to manufacturing, impurities, or possibly the zinc chloride formula used to extend the release of the drug. Thiroloix also made it clear that if Roche decided to return the compound to Ipsen, the company would, as expected, not pursue any further development by itself. However, if Roche provided feasible solutions upon returning the compound, Thiroloix hinted that the company would consider pursuing future development of the compound (we presume with another partner if Ipsen could prove all of the issues were solved). Roche has since announced its decision to stop development of taspoglutide during the company's 4Q10 earnings call on February 2, 2011.

Questions and Answers

Q: Can you comment on the potential reformulation efforts for taspoglutide? Can you provide any color on how this process is going?

A: Well, as you all know, the issues regarding taspoglutide are elevated rates of nausea and hypersensitivity reactions. Roche has made a number of different hypotheses about these items including the presence of impurities, issues with the manufacturing process, the pH of the product, the peak concentration it generates. There are a lot of leads being followed. Roche has put together a group of experts that have incredible expertise and they have called on our knowledge at Ipsen as well. So, we are working hard to address these issues, and Roche will be communicating their decision when the issue their year-end results. We know as much as you do. One of several decisions can be made. If in their exploratory work, they identify the problem as with taspoglutide itself, there will be no product. This is just one of the scenarios, and we don't consider it likely. The other extreme is that they solve the issue and everything is fine. We will just move forward from there with trials. If they decide from a timing, resource, or priority perspective that they do not wish to continue to develop the product and return it to us, we will not continue to develop it ourselves. It is just not within our scope. But if Roche established that there was a way to solve the problem and still return it to us, we will look at what we can do. But from our perspective, its all upside form here since Ipsen is not responsible for any more costs with taspoglutide development.

ISIS PHARMACEUTICALS

B. Lynne Parshall (COO and CFO, Isis Pharmaceuticals, Carlsbad, CA)

Few updates were provided on Isis' metabolic compounds by CFO B. Lynne Parshall. Rather, focus in both the prepared remarks and the subsequent breakout session was centered on mipomersen, the company's LDL cholesterol lowering drug, which Isis plans to submit to the FDA and EMA in 2011 with partner Genzyme for the treatment of familial hypercholesterolemia. As a reminder, Isis is currently developing four type 2 diabetes therapies: 1) ISIS-113715 (PTP-1B inhibitor, phase 2); 2) ISIS-GCGR (glucagon receptor antagonist, phase 1); 3) ISIS-SGLT2 (SGLT-2 inhibitor, phase 1); and 4) ISIS-GCCR (glucocorticoid receptor antagonist, preclinical). The company also announced last week that its first obesity candidate (ISIS-FGFR4Rx, FGFR4 inhibitor) would begin phase 1 trials in 1H11 (see January 6, 2010 Closer Look). Of interest, during her brief overview of the metabolic pipeline, Parshall noted that phase 1 data for ISIS-SGLT2 would be reported in 2011 and expressed excitement over ISIS-GCGR's potential to improve glucose

control through inhibition of glucagon action in the liver and through positive effects on islets (something we had not heard previously from the company). Finally, although six candidates were highlighted as advancing in clinical development this year, we were disappointed that none of these compounds appeared to belong to the metabolic pipeline.

Questions and Answers

Q: Given that you now have 24 candidates in your pipeline, how do you go about prioritizing what to pursue?

A: Because our business strategy is to achieve phase 2 proof of concept and then look to out-license our compounds, our prioritization actually takes place before the compounds enter preclinical and clinical studies. We don't expect the ones we end up picking to fail through phase 2 proof of concept. We spend a lot of time looking at different targets, both at our target sanction stage and development candidate stage. What I mean is that our anti-sense platform is a phenomenal tool to look at a wide range of targets so that we can pick the ones that we think are the best. For example, if you wanted to target a phosphatase, you can make an anti-sense compound for every single one of them, run them in animals, and pick the one that is the best.

Q: You talked about generation 2.5 chemistry last week. Can you talk about how the RNA gets into the cells and how difficult this process is?

A: Generation 2.5 does not help get the drug into cells any better than generation 2.0 chemistry. Our drugs bind to mRNA. Generation 2.5 involves chemical modifications that make our compounds bind more tightly to mRNA. Once it gets to its target, more of the drug will bind and this binding will be longer in duration. These effects make the drugs more potent. It is not that more drug gets into the cell with generation 2.5. The drugs get distributed throughout the body and get to cells by binding with low affinity to a bunch of different circulating proteins in the body. Because the binding is low affinity, they are easily displaced and have no effect on the function of those proteins.

Q: How does the drugs get into cells though?

A: We do have a hypothesis about this, but this is beyond my expertise. However, I can say that it is not a passive process; it is an active transport process.

KERYX

Ron Bentsur (CEO, Keryx, New York, NY)

In the breakout session, Keryx Pharmaceuticals CEO Ron Bentsur stated that the company has given away the rights for the diabetic nephropathy drug KRX-101. To the best of our knowledge, they have not disclosed who has the rights as of yet.

LEXICON PHARMACEUTICALS

Arthur Sands (CEO, Lexicon Pharmaceuticals, The Woodlands, TX)

CEO Arthur Sands provided an update of Lexicon's pipeline, focusing heavily on its lead program - LX4211, its dual SGLT1/SGLT2 inhibitor candidate. As a reminder, LX4211 treatment showed promising glucose-lowering effects as well as favorable trends in other metabolic parameters including triglycerides, blood pressure, and weight in a phase 2a study (please see January 20, 2010 Closer Look*), and was demonstrated to increase GLP-1 and PYY in a recent PK/PD study (please see January 7, 2011* Closer Look*). Management suggested that the inhibitory effect of LX4211 on SGLT1 is responsible for the observed changes in GLP-1 and PYY secretion. Subsequently, when Sands provided an overview of the competitive landscape, he emphasized that LX4211 is the only candidate targeting both SGLT1 and SGLT2, thereby differentiating it from competitor drug candidates. New to our knowledge, Lexicon will be initiating a drug-drug interaction (DDI) study in 1Q11 investigating the potential interactions between LX4211 and metformin in order to demonstrate the safety of LX4211 use in combination with metformin, and to further characterize the GLP-1 effects of LX4211. Sands reiterated that the company intends to initiate a phase 2b trial in 2Q11, following the DDI study. On LX4211, Sands stressed, "we have a real opportunity there and we will be pursuing it*

aggressively." Although the specific partnering timeline for LX4211 has not yet been established, we speculate that Lexicon will likely seek a global licensing deal for the compound, given management's stated interest to pursue such deals for primary care indications.

- **As a reminder, LX4211 treatment had promising glucose-lowering effects as well as favorable trends in other metabolic parameters including triglycerides, blood pressure, and weight in a phase 2a study, and was demonstrated to increase GLP-1 and PYY in a more recent PK/PD study.** In the four-week, double-blind, placebo-controlled phase 2a study, patients on placebo, patients receiving 150 mg LX4211, and patients receiving 300 mg LX4211 experienced mean A1c reductions of 0.49%, 1.15%, and 1.25% from baselines of 8.20%, 8.22%, and 8.50%, respectively. LX4211 treatment was well tolerated, the rate of adverse events was comparable to placebo, and no UTIs were observed (for more information, please see January 20, 2010 *Closer Look*). More recently, Lexicon released results from its PK/PD study demonstrating that LX4211 treatment brought about significant increases GLP-1 and PYY secretion compared to control (please see January 7, 2011 *Closer Look*).
- **Sands provided an overview of the competitive landscape, noting that LX4211 is the only candidate targeting both SGLT1 and SGLT2.** Other companies with SGLT2 inhibitor candidates in development include: BMS/AZ (dapagliflozin), J&J (canagliflozin), Astellas Pharma (ASP-1941), Boehringer Ingelheim (BI-10773), Chugai/Roche (tofogliflozin), Taisho (TS-071), and GlaxoSmithKline (GSK-1614235), and Pfizer.
- **On a more speculative note, we have heard that there are labs targeting SGLT3 as well and would like to learn more about this**. As we understand it, UCLA researchers and their colleagues characterized the function and tissue distribution of a protein encoded by the SGLT3/SLC5A4 gene, which is a member of the sodium/glucose transporter gene family (SLC5). Expression studies indicate that human SGLT3 (hSGLT3) is expressed in human skeletal muscle and small intestine, particularly in cholinergic neurons in the submucosal and myenteric plexuses. Functional studies using the Xenopus laevis oocyte expression system showed that hSGLT3 was incapable of sugar transport, even though it is membrane-bound. Electrophysiological assays further revealed that glucose caused a specific, phlorizin-sensitive, Na+-dependent depolarization of the membrane potential. Uptake assays under voltage clamp showed that the glucose-induced inward currents were not accompanied by glucose transport. These results suggest that SGLT3, although a family member of glucose transporters, is a glucose sensor in the plasma membrane of cholinergic neurons, skeletal muscle, and other tissues. It would be interesting to understand the extent to which this is interesting to companies developing compounds in this class.

Questions and Answers

Q: Do you intend to partner for LX4211 before, during, or after your upcoming phase 2b trial?

A: As you might expect, the discussions we're having are heavily data-driven. With every new piece of data, we actually see things catalyze in a different direction. In particular, our recent data with GLP-1 has been catching additional attention. We have been careful not to model partnerships in our financials for the next 12 months, to provide a conservative estimate for our financials. If the right partnership presents itself, we would definitely consider it. If not, we'll evolve our phase 2b study and then look at partnership opportunities for phase 3.

Again, I just want to reiterate that the latest data is very intriguing, because there has been a lot of interest in GLP-1 secretagogues in the industry (e.g. with exenatide). There have been early deals with GPR119 agonists, which people are hopeful will trigger GLP-1 release.

Q: Can you comment on the design of the phase 2b study? Will it be a three-month study or a six-month study? How many patients do you intend to enroll?

A: It will be a three-month study, which is the standard timeframe for phase 2b studies. Currently, we're examining the potential to use this compound on top of a background of metformin. Some of this is driven by partnership discussions we're having. Metformin is a compound that is widely described, and is generic. There

has been some recent data that indicates metformin may have some interesting GI effects as well, some of which may operate through the GLP-1 signal. In our drug-drug interaction study, we aim to demonstrate LX4211 is safe in combination with metformin, and we aim to investigate some mechanistic parameters such as GLP-1. It would be a short study that would be conducted before the phase 2b study that would enable us to use LX4211 on top of metformin. Metformin plus placebo would be the control arm, and we would investigate three doses of LX4211. We anticipate enrolling approximately 60 patients in each arm.

Q: You didn't see any urinary tract infections (UTIs) in your phase 2a study. What gives you confidence that this will hold in future studies?

A: To some extent I think it will be a class effect. The question really is how big of an issue it will be. What was pretty clear in our phase 2a study was that a clear downward slope exists in the amount of glucose secreted in the urine over time - as patients came under better glycemic control, they spilled less glucose into their urine. We anticipate that patients can get down to their baseline level of glucose secretion of about 17g per day. Hopefully patients will be able to get down to a similar risk for UTIs that they had before starting LX4211 treatment.

Q: Where does LX4211 stand in terms of toxicology studies?

A: We've completed a 13-week toxicology study, and we know what the minimum therapeutic window is. We didn't see any toxicology signals in that study, so we're going to need to use significantly higher doses moving forward. We plan to conduct six-month and nine-month toxicology studies, and we are confident that the mechanism of action is safe.

Q: What will the effects be of using LX4211 in combination with metformin?

A: Metformin will not change the amount of glucose excreted in the urine, but rather will just make blood glucose go down faster. Metformin provides the benefit of additional glycemic control.

MANNKIND

Alfred Mann (CEO, MannKind, Valencia, CA)

MannKind founder and CEO Alfred Mann provided valuable nuances on a number of aspects regarding Afrezza, which he believes has "blockbuster or super blockbuster potential." First and foremost, Mann remained "cautiously optimistic" on the upcoming FDA decision. He noted that the new Dreamboat inhaler reduces the amount of coughing, while delivering the same amount of Afrezza to the deep lung as the previous MedTone inhaler. Two inhalers would be provided with each month's supply of Afrezza. Regarding manufacturing capacity, Mann stated that each machine will be able to produce enough Afrezza to treat approximately 150,000 people, so by the end of the year, MannKind will have the capacity to produce enough Afrezza to treat 400,000 to 500,000 people assuming the company gets three machines up and running as planned. At full capacity, the manufacturing facility would have the ability to produce enough Afrezza to treat roughly two million people. In efforts to prepare for Afrezza's eventual launch, studies are underway to expand claims for the drug, including treat-to-target, insulin intensification, and head-to-head trials. During Q&A, Mann revealed that the number of partnering discussions the company is engaging in has actually increased since last summer, and MannKind will likely not narrow the list down until the label is better defined so potential partners can define the opportunity more effectively. On pricing and reimbursement, Mann noted that Afrezza will likely be able to get into tier 2 within six months of approval if it is priced within 5% or so of Novolog and Humalog. In addition, he reviewed the issues raised by the FDA in the Complete Response Letter. Notably, one investor caused a stir by being very rude to Mr. Mann; he apologized after realizing his claim about disclosure was unfounded.

- **Alfred Mann emphasized that Afrezza is the first in a new class of ultra-rapid-acting insulins, with "blockbuster or super blockbuster potential."** Citing our Close Concerns Diabetes Close Up ADA Healthcare Professional Survey, Mann noted that an increasing percentage of HCPs surveyed from 2008 to 2010 would use Afrezza in their practices - 28%, 48%, and 95% in 2008, 2009, and 2010, respectively. Mann expressed his belief that the baggage from Exubera is fading. Additionally, he was confident about the safety of Afrezza, as they have not yet seen any

safety signal, but rather, only small, clinically insignificant changes in pulmonary function. Furthermore, there appears to be significant interest building among the medical community. In a survey of doctors (a balanced sample of PCPs and specialists in the US and Europe), a sizeable proportion said that they would prescribe Afrezza to their type 1 patients(~25-45% of respondents) and to their type 2 patients (~20-30% of respondents). Mann believesthat once approved, Afrezza will be used earlier and earlier in the treatment of type 2 diabetes, although that remains to be seen.

- **Alfred Mann also reviewed the issues raised by the FDA in the Complete Response Letter.** He confidently stated that there were no safety concerns to his knowledge. The CRL focused on: 1) the clinical utility of Afrezza; 2) bioequivalence of the new device; and 3) questions surrounding the new device - how to use it in a clinical situation, show that it can be used for two weeks, and demonstrate that it has the same performance at the beginning and the end. During the Q&A session, an enraged investor chastised Mann for failing to disclose that there was a clinical utility issue with study 009 mentioned in the CRL. Mann responded that they did indeed refer to the company's pivotal type 1 study (009) in their statement. Still unhappy, the same investor later questioned why it took so long for MannKind to let investors know that they had received a CRL from the FDA (using the Freedom of Information Act he found out that the company had received the news four to six days prior to letting its investors know). After the Q&A session concluded, we overheard another investor asking the disgruntled individual how it went, and he responded, "I feel like throwing up."

Questions and Answers

Q: Can you comment on the status of labeling discussions with the FDA for Afrezza?

A: They said that they would let us know in approximately four weeks from our scheduled PDUFA date whether or not Afrezza will be approved, so there are still two weeks left for labeling discussions. It would be unusual for them to discuss labeling this early. They have had us prepare a number of tables which appear like they would be used in the label, but we have not had any explicit discussions with the agency about labeling as of yet. It is my understanding that labeling discussions only take a few days at most.

Q: I just wanted to confirm that you mentioned there is less cough with the new inhaler.

A: We have indeed seen less cough because the new inhaler doesn't cause any agglomerates to form.

Q: What clinical data would I reference?

A: In the studies where we compared the MedTone with the Dreamboat, we conducted a direct crossover looking at change in pulmonary function over time. With the switch to the Dreamboat, we saw an acute change. It reduced the amount of large particulate matter, maintaining the same amount of drug delivered to the deep lung while reducing the incidence of coughs.

Q: Given the reduced amount of coughing and fewer aggregates with the new device, is it possible that the deposition of Afrezza is different in the lung? (And would long-term safety studies need to be conducted if this is the case?)

A: I think your logic is somewhat clouded. It's exactly the same formulation, as the same fraction is inhaled into the deep lung. The science and the data confirm bioequivalence, which means we have effectively maintained the same formulation. The same amount of powder gets into the lung, and only remains there for a short period of time no longer than a few hours. The bottom line is that what gets into the throat is different, but what gets into the lungs is the same. In the old inhaler, some of the powder didn't get out of the cartridge, so some times patients would even have to do two inhalations.

Q: In November you mentioned that most of the discussion is around the bioequivalence of the new device. Would you say that safety and efficacy are comfortably behind us?

A: The CRL didn't raise any safety issues at all. To my knowledge there have been no additional discussions around safety. The CRL focused on: 1) the clinical utility of Afrezza; 2) bioequivalence of the new device; and 3) questions surrounding the new device - how to use it in a clinical situation, show that it can be used for two

weeks, and demonstrate that it has the same performance at the beginning and the end. In terms of where we've been - we've been audited and inspected, and look forward to the results.

Q: When you got your CRL, did the FDA say anything about the 009 study?

A: What they said was that based on ANCOVA LOCF analysis, we were at the very limit of the 0.4% tolerance for non-inferiority. They now use other ANCOVA technology and we're at 0.37%. We're OK. We also added the 117 trial, which showed that we actually had a somewhat better A1c than Humalog.

Q: If you get a second CRL, are you going to tell us about things like this earlier? It took us three months to find out that there was a clinical utility issue with the 009 study.

A: We said that early. They wanted us to explain how the product would be used in the treatment of diabetes. We analyzed therapies for type 1 and type 2 and gave them a whole analysis for how long you would use the product.

Q: How long was the CRL? How many pages was it?

A: There were a lot of things in the CRL. I don't remember specifically - six or eight pages I think? It was several pages. A lot of it was standard boilerplate. The agency talked a lot about the fact that they didn't like the marking on the old MedTone. They're happy with what we have on the Dreamboat. They wanted an update on safety information because we had not given them an update for a year since we filed originally. They commented on the REMS program, and we hadn't yet come to an agreement. Things like that were not significant.

Q: Just to confirm - you'll have the capacity to produce enough Afrezza to treat 500,000 patients by the end of 2011.

A: If you run the machines 24/7, they produce enough to supply 192,000 patients each. However, we are not going to run the machines 24/7. There is down time. It'll probably end up being somewhere on the shy side of 150,000 per machine. One machine has already been installed and qualified, and will be moving to go to validation as soon as we know where we are. We have two more machines on order to be installed later this year. So, we should have the capacity to produce enough Afrezza for between 400,000 and 500,000 patients by the end of 2011. The fully equipped factory will be able to treat about two million patients.

Q: If you are to gain approval, when is the earliest you will launch?

A: We can't really say that because the first step as soon as we get the label defined is to sit down and select a partner, which will take several months. The partner will to a large extent define with us the launch scenario so I don't think we can speak authoritatively about that just yet.

Q: There was a time this past summer when you were talking to six partners. You mentioned that it will only take a few months after approval to nail down a partner. Have you narrowed it down from the list of six? Can you say?

A: Actually, there are a larger number we're talking to now. We haven't really narrowed it down. All the potential partners want to wait to see what the label is and what the opportunity is so they can define the program more effectively.

Q: You've made comments that Afrezza will be priced within 5% of Novolog and Humalog. In discussions I've had with a pharmacist, he indicated that Afrezza would be quite a bit more expensive. Can you comment on the pricing differential and how confident you are about where its price is relative to others?

A: How can your pharmacist know what it's going to be priced?

Q: Through reverse engineering.

A: The bottom line is that we have had meetings with the gatekeepers who insure about 30% of American lives. The consensus is that if we're within 5% or a little bit more that we should get into tier 2 within six

months. That's the goal we have and that's what we think the price should be. Again, our eventual partner will play a major role in the pricing decision.

Q: Can you provide any insight on why the FDA needs four more weeks? Is it simply their year-end backlog, or do they need more information?

A: I can't say that it's a year-end backlog for sure. There were a number of things that they were in the process of doing through December, and I'm guessing they just didn't have it all done given the holidays. They also did some fieldwork in addition, and had to get it all done and get the reports in. They're being very thorough, particularly here where there has been a fair amount of controversy. We are pleased they are being so thorough, but again, they did not provide a specific reason for the delay.

Q: In a recent interview, you said that an audit at one of your facilities took two weeks instead of two days. You said that without reading more into it, that it was an optimistic sign. Why did they take so long?

A: It was an inspection of the site responsible for the 142 bioequivalence study. Since we changed devices they wanted to make sure they thoroughly investigated that study so they spent a couple weeks doing it. That's a long time, but they were being exceedingly thorough, as they should be.

Q: You've [Mann] been an active purchaser of stock over the last month, having already been a large shareholder. Why did you feel the need to buy stock over the last three to four weeks?

A: I own something like 44% of the company, and we're selling more shares every week. I simply didn't want to dilute my share. Every time other major holders buy more shares, I buy the same number of shares.

Q: Using the Freedom of Information Act, I found out that you got a response from the FDA on the 10th of March last year for your CRL, but you held your call much later, on the 16th.

A: I think we got the letter on the 12th.

Q: I'm just trying to understand - somewhere in the letter, it mentioned that the 009 study failed. When I read through your transcript (which is about a page or two long), it doesn't mention anything about 009.

A: We did discuss our pivotal type 1 study, which was 009.

Q: You briefly touched on other Technosphere formulations that may be coming soon. Can you comment on Technosphere as a delivery vehicle? What else are you looking at?

A: We're not pursuing any other Technosphere formulations any time soon - they're all early-stage programs. The significance of the Technosphere technology is that it can stabilize large or small molecules, and enable quick delivery into the arterial system. When you're talking about natural hormones that operate in spikes, they'd be delivered better with this technology. If you're talking about a drug that you would like to get into the brain quickly (e.g. migraine medications), we could get it into the arterial system within minutes. We're talking to a number of outside people, and we also have several molecules of our own that we're working on. There are interesting opportunities, but they're all in early stages, and will not happen for a few years.

MEDTRONIC

Bill Hawkins (Chairman and CEO, Medtronic, Minneapolis, MN)

In his last JPM presentation as Medtronic CEO, Mr. Hawkins shared his parting thoughts on Medtronic's progress over his four years at the helm and its prospects in the near future. His points of pride included clarifying the company's focus on chronic disease, replenishing the pipeline, shifting resources to emerging markets, and "the thing I'm most proud of" - helping to build Medtronic's current management team. Although diabetes was not a major focus of the presentation, Mr. Hawkins noted that the company is number one in both insulin pumps (a $2.1 billion market) and CGM (in which Medtronic had a 48% growth rate for FY10, with "tremendous head room" remaining in the future). Unlike his characterization of other markets, he did not forecast market size of CGM or give the company's standing. During the breakout session, he said that Medtronic expects to release a new line of durable pumps in FY13, and targeted the

company's patch pump for the first half of FY13. (As recently as the company's F1Q10 earnings call in August 2009, management was slating the patch pump's launch for FY2011.)

Questions and Answers

Q: Could you give a status update on your insulin patch pump? Also, when will be the launch of the replacement for the Paradigm line?

A: I don't know if we have a current projection for the patch pump. All the companies in the arena have had setbacks - I don't know if that's the right word. In discussions with the FDA, more and more is being required before market. That's impacted us like it's impacted everyone. I don't know about the timeline; I still believe we're on a timeline relative to everyone else such that we will be very competitive with our patch pump with whoever else is out there. As for the Paradigm replacement, we have a next-generation pump in development scheduled for FY13.

Mike Weinstein (JP Morgan analyst, session moderator): The patch pump has been announced for launch in the first half of FY13.

Q: Will the changes in the 501(k) process be negative, neutral, or positive for business conditions in 2011?

A: Good question. (Pause.) I think it will be neutral to slightly negative.

Q: Do you want the bar to go up?

A: No. I think our industry is an ecosystem that requires different levels of players. At the end of the day, I want to see this country maintain its strong competitive advantage in medical innovation. If as a big company I have to give up what I'd gain (in terms of market share) by stronger barriers, I'd rather have the barriers and smaller innovative companies that give us a chance to partner or advance (the US) position on the global landscape.

MERCK

Ken Frazier (President and CEO, Merck, Whitehouse Station, NJ)

President and CEO Ken Frazier described Merck's growth strategy going into 2011, frequently mentioning the Januvia franchise and diabetes in general. He referred to the FDA's (hours-old) decision to review the NDA for Extended Release Janumet. He also noted Januvia's ongoing launch in Japan as well as its growth to become the number-one oral antidiabetic drug in the Asia-Pacific region after just two-and-a-half years of availability there. (On a related note, Frazier mentioned that over 75% of the worldwide diabetes population resides in developing markets - one of many therapeutic issues where he believes Merck can help people in these markets). Merck's recent acquisition of SmartCells was mentioned as the most recent of the company's "46 significant deals with external partners" in 2010 (for our coverage of the deal, see the December 16, 2010 Closer Look), and diabetes drugs were displayed in the company's most updated late-stage pipeline: MK-3102 (new to phase 2 since our 3Q10 coverage in the November 2, 2010 Closer Look) and sitagliptin/pioglitazone (still in phase 3). We were disappointed that no breakout session was provided for this presentation although we believe this relates to Reg FD, disclosure, and how various companies interpret SEC rules about the "quiet period" - other large pharmaceutical companies such as Novo Nordisk do not present at the conference for this reason.

METABOLIC SOLUTIONS

Stephen Benoit (CEO, Metabolic Solutions, Kalamazoo, MI)

In between the presentations at J.P. Morgan, we had the opportunity to meet with Metabolic Solutions, a company developing novel PPAR-sparing insulin sensitizers for the treatment of type 2 diabetes. According to CEO Stephen Benoit, the insulin-sensitizing effect of PPAR gamma agonists (such as GlaxoSmithKline's rosiglitazone and Takeda's pioglitazone) is not mediated through activation of PPAR gamma, but rather through a mitochondrial target that plays an important role in the coordination of cellular metabolic pathways that Metabolic Solutions has since identified. In fact, the company's research shows that PPAR

gamma activation may actually cause the fluid retention, edema, weight gain, and bone loss observed with the above TZDs. Since this discovery, Metabolic Solutions has developed two compounds that activate this unspecified mitochondrial target and completely avoid PPAR gamma. The company's lead compound MSDC-0160 is an isomer of a metabolite of pioglitazone and was shown to lower fasting glucose, raise HDL, and decrease blood pressure at comparable levels to pioglitazone over 28 days in individuals with type 2 diabetes (n=76). Additionally, unlike pioglitazone, treatment with MSDC-0160 did not lead to weight gain and fluid retention. The company is currently conducting a phase 2a study (n=420) that is expected to report in 3Q11. Metabolic Solutions is also developing MSDC-0602, a new chemical entity that also activates the above mitochondrial target. In a phase 1a/1b trial, repeat dosing over a seven-day span was found to be safe. The company plans to initiate a 28-day phase 2 trial shortly in individuals with type 2 diabetes. Overall, we found ourselves intrigued by the company's scientific evidence and clinical data for its candidate insulin sensitizers, and we look forward to hearing the results from the ongoing phase 2 trial for MSDC-0160 later this year.

OREXIGEN

Mike Narachi (CEO, Orexigen, San Diego, CA)

CEO of Orexigen Mike Narachi presented a brief update of the company's development and commercial strategy for Contrave and Empatic. Because of the proximity to the PDUFA date (January 31, 2011), Orexigen did not hold a breakout session. Interestingly, Narachi provided expectations of a complete response letter that addresses the "usual things," such as labeling, REMS, and details of post-approval outcomes study. He also noted that the track record for this division is to approve drugs, on average, eight months after the PDUFA date. Nevertheless, Orexigen plans to launch Contrave in North America with Takeda this year. Outside North America, however, Contrave remains unpartnered; management suggested they are "gauging interest" in 8-10 potential partners and plan to provide an update on the structure and timing of a partnership in 1Q11 or 2Q11. Narachi was also pleased to report that the company would not be looking for any additional funding in the "foreseeable future." Lastly, Orexigen hopes to begin moving its second obesity compound, Empatic, forward in 2011 by conducting an end-of- phase 2 meeting, beginning phase 3 planning, and securing a partnership (Empatic is a combination of bupropion and zonisamide that completed phase 2 development in 2009). According to the company's timeline, Empatic is currently scheduled to begin phase 3 trials in 2012; however, we look forward to a more detailed update on this compound.

- **As for positioning Contrave, he emphasized a three-step approach to focus on patients who respond to therapy:** 1) screening (for appropriate BMI, potential to adhere to lifestyle change, and inadequate response to diet/exercise); 2) 16-week "therapeutic trial" (advance only those who respond [>5% weight loss] and adhere to Appropriate Use Guidance); and 3) long-term therapy. We are particularly interested in the company's proposed cardiovascular outcomes trial, which is a large simple trial (LST).

PERRIGO

Joseph Papa (CEO, Perrigo, Allegan, MI)

During a wide-ranging discussion of Perrigo's recent successes and future plans, Mr. Papa said that the company is considering store-brand blood glucose monitoring as an area of future development.

Questions and Answers

Q: Can you elaborate on your interest in blood glucose monitoring? Any plans for partnering in the near future?

A: At this time, we can only say that we are interested in looking at blood glucose monitoring.

PFIZER

Geno Germano (President and General Manager of Specialty Care and Oncology, Pfizer, New York, NY)

Pfizer President and General Manager of Specialty Care and Oncology Geno Germano focused primarily on the company's prospects in his business unit, making little mention of diabetes during the presentation. Germano briefly reviewed Pfizer's "Invest to Win" areas which were initially announced in January 2010; interestingly, "diabetes" has been replaced with the more broad category "metabolic disorders" as an area of focus (other "Invest to Win" areas include neuroscience, pain/inflammation, infectious diseases, and oncology). Although not anything new, it was nice to hear Germano mention that Macugen has been submitted for EMA review for a diabetic macular edema (DME) indication (please see November 8, 2010 Closer Look *for more information). During the subsequent Q&A session, Chuck Triano, Pfizer SVP of Investor Relations assured us that Pfizer is committed to developing therapies for diabetes and other metabolic disorders, even though the company does not currently have any late-stage compounds in the area.*

Questions and Answers

Q: Today's presentation focused heavily on oncology and specialty care. Could you provide an update of your pipeline for diabetes and metabolic disorders?

A (Chuck Triano, SVP of Investor Relations): We didn't provide any updates today on the pipeline for diabetes and other metabolic disorders, because there weren't any to present. Everything we have in this area is still early-stage. It's really an area we need to improve in. It's one of our stated "Invest to Win" areas. Even though we don't have any updates for you today, please rest assured that we are still committed to investigating therapies in this area.

REATA

Warren Huff (CEO and President, Reata, Irving, TX)

Reata CEO and President Warren Huff reviewed the company's lead compound, bardoxolone methyl, an oral antioxidant inflammation modulator for the treatment of chronic kidney disease (CKD) in people with type 2 diabetes. He focused especially on the company's most recent phase 2b study (n=227). Patients receiving bardoxolone methyl underwent a significant improvement in estimated glomerular filtration rate (eGFR) at 24 weeks compared to standard of care (roughly 10 ml/min/1.72 m2 compared to negligible change in standard of care). Bardoxolone methyl patients were also significantly more likely to undergo improvements in CKD disease stage (60% vs. 17% for standard care) and significantly less likely to regress in disease stage (4% vs. 13%). The most common adverse event in the bardoxolone methyl group was muscle spasm at a rate of 49%; Huff noted that the spasms (usually nocturnal calf cramps of mild to moderate intensity) typically resolved within four to eight weeks. Full-year data are now being analyzed and are likely to be presented at this year's ADA meeting in June. Management plans to initiate a 1500-patient phase 3 trial in 1Q11. The outcomes-based trial is expected to complete in the second half of 2012, which would enable Reata to launch bardoxolone methyl as early as 2013. The company has licensed bardoxolone methyl to Kyowa Hakko Kirin in Japan, China, and Southeast Asian markets and to Abbott in Europe and other international markets; Reata retains US commercialization rights.

REGENERON

Leonard Schleifer (CEO, Regeneron, Tarrytown, NY)

CEO Leonard Schleifer provided an overview of Regeneron's pipeline, highlighting its VEGF Trap-Eye therapy, which is being explored as a treatment option for diabetic macular edema (DME), amongst other indications. Most of the discussions on VEGF Trap-Eye centered on its potential indications for wet age-related macular degeneration (AMD) and/or central retinal vein occlusion (CRVO), as phase 3 trials for those indications have reported are reporting soon, and could receive approval as early as 2012. Even so, Schleifer acknowledged that DME might ultimately be a bigger opportunity than AMD. He cursorily reviewed the one-year phase 2 data that was recently released, which demonstrated significant improvements in visual acuity with VEGF Trap-Eye treatment compared to laser therapy, the current standard of care. Although no specific timeline was disclosed, Schleifer noted that the company is in the planning stages for phase 3 studies for the use of VEGF Trap-Eye to treat DME. In addition, he stressed that

VEGF Trap-Eye would only need to be injected bimonthly, a large benefit over ranibizumab, Roche's [US]/ Novartis' [OUS] once-monthly Lucentis.

Questions and Answers

Q: What will be presented at the upcoming meeting in Miami?

A: We will be presenting a full readout of the age-related macular degeneration VIEW 1 and VIEW 2 studies, the CRVO study, and the DME study.

Q: What about CATT trial [a head-to-head comparison of Lucentis and Avastin treatment on age-related macular degeneration] data?

[Laughter from the audience]

A: We will not be presenting that.

Q: Do you see the potential somewhere down the road for quarterly, or even biannual dosing?

A: Not with this product. I think we have the dosing/timing right with this product. Lifecycle management and alternate formulations are a totally different issue we'd have to consider further down the road.

Q: For the treatment of AMD in the US, 60-65% or so use Avastin off-label, while the remaining 35-40% use Lucentis. How do specific doctors choose which to administer? Also, how do you view your market opportunity in this context?

A: In some respects, we don't care. We want to take market share away from both. Both the FDA- approved Lucentis and the unapproved but nationally tested Avastin require a shot in the eye every month. In contrast, VEGF Trap-Eye would only need to be taken once every eight weeks, and would hopefully be covered by Medicare. We would like that to be the discussion. Granted, the therapy would not come without risk, discomfort, etc., but if we do this right, we should be competing against both Avastin and Lucentis. To go back to your first question, some doctors tell us that they choose Lucentis because they believe it means something that the FDA has tested and done quality control. Doctors are well aware that what you get from one compounded pharmacy for Avastin is not the same as another, simply because quality control and pharmacovigilance are not there. This is a dangerous path we somehow got down.

Q: As it relates to partnerships, obviously sanofi-aventis has been good for your company (and lucrative), but you decided to raise money at the end of last year. Why?

A: You're referring to our secondary offering of $175 million. sanofi-aventis participated, and actually took about 20% of that offering. The reason we did so is because VEGF Trap-Eye is such a unique opportunity. Only a trivial amount of product is required, so we can manufacture all that we need by ourselves. There are a limited number of retinal specialists, so we could access most of them with a salesforce of 100. Genentech was able to do it [with Lucentis] and grow it to a one billion dollar product. Hence, we raised money to launch VEGF Trap-Eye by ourselves, as we think we will be better off financially. It really is rare that you have 100% of control in a multibillion-dollar market...

Q: How are you going to commercialize VEGF Trap-Eye?

A: As I said, there is a run rate of approximately $1.6 billion in the US. If two-thirds of all people with AMD in the US are being lost to Avastin, the real opportunity is somewhere around $5 billion. About 1200 doctors do most of the prescribing, so we could reach them with a salesforce of about 100. Frankly, most of the marketing will be done at medical meetings. Retinal specialists are quick to adopt. The proof of the pudding is that two-thirds are treated with Avastin, which had no marketing at all. Doctors will figure out that VEGF Trap-Eye is better for patients, as it is safer and imposes less of a burden. If we come out with fair pricing for the drug, I think there will be a bias towards it, which we will supplement with our own marketing efforts. Outside of the US, we have a great partner, Bayer. We'll engage in an even 50/50 profit split, even though they'll be doing the lion's share of marketing.

Q: Regarding the DME opportunity for VEGF Trap-Eye, what are your initial thoughts on how you would design a phase 3 study, given there are caveats with that difficult population?

A: The DME indication is a very important one that will be as large or larger than the indication for age-related macular degeneration. However, the regulatory requirements are somewhat disconnected. Outside of the US Novartis managed to get Lucentis approved with two small studies in Europe. In contrast, the US requires two-year endpoints with three years of follow up. We may have to take one approach with Bayer outside of the US, and a different approach in the US. We have to figure out if we're going to have to do a head-to-head comparison with Lucentis or not. We need to have more discussions with regulatory agencies. We plan to start them this year.

REGULUS THERAPEUTICS

Kleanthis Xanthopoulos (CEO, Regulus Therapeutics)

CEO of Regulus Kleanthis Xanthopoulos provided a detailed presentation on the company's scientific platform as well as lead products in development. There was no mention of the company's work in metabolism and cardiovascular disease; however, one slide indicated that it remains an important therapeutic area of interest. As we understand it, candidates for metabolism are still in the discovery/ exploratory stage. Xanthopoulos focused the majority of his remarks on lead candidates for fibrosis and oncology, which remain in preclinical stages and are scheduled to enter into the clinic within 12-24 months.

RESMED

Kieran Gallahue (President and CEO, ResMed, San Diego, CA)

After emphasizing the importance of treating sleep-disordered breathing (SDB), ResMed President and CEO Kieran Gallahue sized the market opportunity, reviewed ResMed's latest product offerings for the treatment of sleep apnea, and discussed the healthcare economics of such products. Recent epidemiological data presented by Dr. Terry Young found that 20% of the adult population suffers from sleep apnea - 13% have mild sleep apnea (defined as 12 or more stops in breathing during an hour of sleep), and 7% have it in its moderate to severe form. Sleep apnea is prevalent in patients with other serious conditions, and according to Gallahue, it is "right in the middle of the metabolic syndrome." Subsequently, Gallahue elaborated on the relationship between obstructive sleep apnea (OSA) and diabetes, emphasizing the need for people with type 2 diabetes to be assessed for symptoms of SDB. Some research has suggested that OSA may have a causal role in the development of diabetes, and that it is associated with insulin resistance, independently of obesity. As such, it is no surprise that 48% of patients with type 2 diabetes (and more specifically, 86% of obese males with diabetes) suffer from OSA. To raise awareness, ResMed recently teamed up with Joslin to fund a series of seminars to engage endocrinologists and diabetes educators on the link between SDB and diabetes. In addition, Gallahue also pointed out that the market opportunity for ResMed's products will increase along with the increasing prevalence of obesity worldwide.

- **Gallahue reviewed the most recent product offerings ResMed has brought to the market.** The S9 Series of flow generators was introduced about a year ago, with the CPAP line for it following soon after. In addition, ResMed recently introduced the Quattro FX (a full-face mask), and the minimally obtrusive, low-noise Swift FX mask targeted specifically towards women. Gallahue emphasized that new mask offerings are the "backbone of ResMed historically" as the patient interface is the most important part of the experience.
- **In addition, he stressed that treating OSA is cost-effective**, as evidenced by the National Institute for Clinical Excellence's (NICE; a respected independent organization in the UK responsible for providing guidance on healthcare) recommendation for healthcare providers to identify patients with sleep apnea early and treat patients with moderate or severe OSA with continuous positive airway pressure (CPAP). Gallahue also suggested for greater emphasis to be placed on the identification and treatment of sleep apnea for those involved in the transportation industry, given the number of preventable accidents and deaths associated with the condition.

Questions and Answers

Q: While your unit growth is significant, what about your price, especially with the current healthcare environment in the US?

A: We assume a 5% price decrease per annum. I would argue that it's probably been one of the best things that has happened to the industry, forcing companies to think of scale and efficiency.

Q: In an environment where healthcare costs need to come down, what does that mean for ResMed?

A: In my opinion, home care is a critical element that would help to reduce overall healthcare costs. They key is to keep people out of hospitals. If you look at the top five chronic disorders (cardiovascular disease, diabetes, obesity, stroke, and cancer), we're in all of them with the exception of cancer. People talk about telemedicine - well, we've been doing it for five to six years.

Q: As the rollout of competitive bidding occurs, how do you see ResMed managing that?

A: I would first like to point out that 50% of our revenue is in the US, and 50% is outside of the US. I think it's important to recognize the balance we have in our market base. Competitive bidding only pertains to Medicare, which is a percentage of a percent of our business. Sleep-disordered breathing is something that affects people well before they reach Medicare age. With many people becoming obese at younger ages now, there are now a significant number of young adults experiencing sleep-disordered breathing. Back to competitive bidding - it won't go nationwide until 2015, if it ever goes nationwide. There is currently a lot of pushback on the implementation.

Q: Can you talk a little bit about healthcare utilization in the sleep apnea market?

A: We're in a highly underpenetrated market with a lot of room for growth; our growth is probably about 8-10% now. It's definitely slowed down, but it's still positive.

Q: What are your thoughts on the S9?

A: It has been a very successful product launch, and we are extremely pleased about how the market has responded.

Q: Any updates on the GLYCOSA trial?

A: not at this point in time.

ROCHE

Erich Hunziker (CFO, Roche, Basel, Switzerland)

In a packed Grand Ballroom, Dr. Hunziker gave an overview of Roche's position heading into 2011. He focused largely on biosimilar competition to its portfolio of biologics (e.g., Avastin, MabThera/Rituxan, Herceptin, Pegasys, Lucentis -a threat that Roche takes "very seriously"), commitment to long-term innovation, and the company-wide "operational excellence" program ("not a cost-cutting project, a fundamental re-engineering"), which is projected to generate cost-savings in the coming years. Dr. Hunziker favorably mentioned Diabetes Care, calling the unit the first of three pillars that support Roche Diagnostics. He noted that Roche is the market leader in the worldwide "oligopoly" of four BGM companies, and he anticipated the FDA approval of Roche's maltose-independent test strips during 2011. During the breakout session, Dr. Hunziker referred to the patch pump as a "genius move" and said that management would be willing to give more updates on the Solo semi-disposable pump during the company's 4Q10 update on February 2, 2011. (Given that the Solo has been FDA approved since 2009, we have not been certain why the lag is so long between Roche's 2Q10 purchase of Medingo and the previously communicated 2012 launch, though we believe manufacturing capacity plays a role.). On the pharma side, Dr. Hunziker emphasized the strength of Roche's late-stage pharmaceutical pipeline of 14 compounds, including three for diabetes (the once-weekly GLP-1 agonist taspoglutide [phase 3], the dual PPAR alpha-gamma agonist aleglitazar for CV risk reduction in individuals with type 2 diabetes [phase 3], and the SGLT-2 inhibitor RG7201 licensed from Chugai [phase 2]). In its phase 1 program, Roche is currently developing an 11 beta HSD inhibitor (RG4929) and is partnering with Bayhill Therapeutics to develop BHT-3021, a type 1 diabetes vaccine comprised of plasmids encoding proinsulin. Although he did not draw attention to Roche's recent purchase of Marcadia (see December 28, 2010 Closer Look), Dr. Hunziker characterized Roche's array of 150 partners as a strong source of innovations.

- **Although Roche is the worldwide leader in the "oligopoly" of four BGM companies, Dr. Hunziker acknowledged that Roche Diabetes Care is facing difficulty in the US due to the "so-called maltose issue."** (The company's US test strips are susceptible to maltose interference; maltose-independent strips were approved in Europe in 2Q10 and are currently under FDA review.) Dr. Hunziker forecast that the new strips would become available in the US in 2011; he noted that other companies have already overcome this technical issue. Following US release of the new strips, Roche would introduce some of the products that have made it successful in international markets. According to the company's 3Q10 update, these US launch plans include the "sleek" BGM Accu-Chek Aviva Nano (1H11), the integrated lancet/BGM Accu-Chek Mobile (2H11), and the integrated pump/BGM Accu-Chek Combo (1H11). We assume these launch dates aren't necessarily set in stone given the FDA's sluggish pace of late.
- **Roche's once-weekly GLP-1 agonist, taspoglutide, is still listed in the pipeline following the suspension of phase 3 dosing several months ago due to unexpectedly high rates of discontinuation from nausea and vomiting.** (See Closer Look from September 10, 2010 for details). Dr. Hunziker noted that the company has cuts its sales force in response to this setback, which he said would translate to a delay "in the range of 12 to 18 months" for taspoglutide's development. In Roche's 2Q10 earnings call - prior to the announcement of the dosing suspension - management forecasted a 12-to-18-month delay (pushing the date of submission until 2013) in response to hypersensitivity reactions during phase 3 trials. It is unclear whether the shift mentioned today was a further delay or the same one. (See our July 22, 2010 Closer Look.) If the same delay, this is shorter than we had imagined, especially if a new formulation is necessary, which we assume would be the case. In the company's late-stage pipeline update on December 9, Roche management stated that a final decision on taspoglutide will be announced during the company's 4Q10 earnings call, which is set for February 2, 2011.
- **The company's SGLT-2 inhibitor, RG7201, has completed phase 2 studies and was slated for a "go/no-go" decision in 4Q10.** We are not sure whether the drug's mention today indicates that RG7201 will definitely progress to phase 3 or that the decision has been postponed. (For more on RG7201, the dual PPAR alpha-gamma agonist aleglitazar, and the rest of Roche's diabetes pipeline, see our coverage of the company's 3Q10 earnings call in the October 15, 2010 Closer Look.)
- **Noting that Roche takes the threat of biosimilar competition "very seriously," Dr. Hunziker explained that management will henceforth be secretive about its protective measures**. He cited erythropoeiten as an example of Roche's success in warding off biosimilar competition, and he expressed confidence that the company would continue to maintain its strong position in biologics: "I don't know of any company in the world that can produce Herceptin cheaper than we can."

SANOFI-AVENTIS

Chris Viehbacher (CEO, sanofi-aventis, Paris, France)

CEO Chris Viehbacher reaffirmed sanofi-aventis' commitment to its diabetes business and indicated his expectations for the business to be one of the key drivers of future growth for the company. Reflecting this commitment, he emphasized that an important goal of the company over the past several years has been to been to move past its identity as a company that just sells Lantus (the number-one diabetes franchise in the world currently) to a company that is a leader in the diabetes industry. To that effect, Viehbacher stated that sanofi-aventis is aiming to provide diabetes patients with a comprehensive set of diabetes solutions that extends past diabetes treatments into education and prevention programs. He highlighted the company's GLP-1 agonist lixisenatide (phase 3, filing in EU in 2H11 and US in 2H12), GPR119 agonist from Metabolex (SAR260093, phase 2a), and recently acquired blood glucose meters from AgaMatrix (iBGStar and BGStar, which launch in US, France, and Germany in 1H11) as significant steps forward for the company. While few new updates were provided during the presentation and the following breakout session, Viehbacher did

reveal that the iBGStar would be sold in Apple stores, a major accomplishment in our view that will substantially aid in the company's direct- to-consumer sales campaign for the new meter.

- **No updates were provided on sanofi-aventis' broad diabetes pharmaceutical pipeline during the presentation.** As a reminder, sanofi-aventis is currently developing a once-daily GLP-1 agonist (lixisenatide) in phase 3 studies. The phase 3 program, termed GETGOAL, consists of 10 trials, two of which - GETGOAL-L ASIA and GETGOAL-MONO - have reported positive results thus far. Viehbacher indicated that results from the remaining trials should be expected throughout 2011 and 2012 and that the company remains on track to file lixisenatide for approval in the EU in 2H11 and in the US in 2H12. The one-year offset in the US filing is due to the need to file CV safety data from the ongoing lixisenatide CV outcomes study (ELIXA), the results of which are expected in 2013. The company also has a GPR119 agonist (SAR260093) in phase 2a development with partner Metabolex for the treatment of type 2 diabetes (results were expected in 4Q10), a novel non-TZD insulin sensitizer (PN2034) in- licensed from Wellstat that was recently regressed from phase 2 studies to preclinical studies for what we presume to be a safety signal, and a beta cell regeneration therapy (Pancreate) in preclinical studies that was in-licensed from CureDM. Finally, reflecting the company's new holistic approach to diabetes care, sanofi-aventis also has a number of compounds that target diabetes complications including a bradykinin B1 antagonist (FOV2304) for the treatment of diabetic macular edema and a urotensin II antagonist (SAR101099) for the treatment of diabetic neuropathy. We hope to hear updates on all of these diabetes candidates shortly.
- **During the breakout session, Viehbacher briefly addressed the potential of the iBGStar and BGStar blood glucose meters the company plans to launch in the US (iBGStar only), Germany, and France in 1H11, throughout the rest of Europe in 2H11, and in Asia and Latin America in 2012.** He focused most of his comments on the iBGStar, which has the ability to connect directly to an iPhone and turn the phone itself into a blood glucose meter. It was emphasized that the meter will not only offer improved accuracy over other current meters (accuracy up to 10%), but will also allow patients to calculate doses of insulin with the meter (which was cited as the motivation behind approximately 80% of overall blood glucose meter use), allow data from meter to be stored so that patient and physician can look at data over time, and allow integration with other possible iPhone applications that help improve diabetes self-management (e.g., apps that help users count calories and carbohydrates). Notably, Viehbacher indicated that the iBGStar would be available for purchase in Apple stores - in our view, a major accomplishment that should substantially enhance the ability of sanofi- aventis to reach consumers directly (although presumably there would need to be a mechanism to ensure strips would be covered by formularies - we aren't sure about the details). Additionally,while the company is trying to diversify its diabetes business, it was made clear that the motivation underlying the partnership with AgaMatrix over the iBGStar and BGStar was to drive sales of Lantus. Finally, Viehbacher stressed that he sees exciting potential in developing mobile- based educational, motivational, and communication tools to improve outcomes and care in many disease areas given the fact that most people throughout the world own mobile phones.
- **As in previous statements made by the company, Viehbacher emphasized that the regulatory pathway still poses significant challenges for biosimilar products, especially in Western Europe and the US.** Furthermore, he underscored that there will be issues related to capacity, quality, and devices that will need to be addressed by the companies producing biosimilar products if they wish to compete effectively for market share around the world. In an important argument in our view, Viehbacher pointed out that Lantus is doing very well against biosimilar competition in India. He noted that sanofi-aventis has the capacity to produce insulin products locally in emerging markets and that it is developing this capacity further (e.g., a new Lantus plant is being constructed in China). Importantly, this capacity allows the drugs to be manufactured and sold at local prices thereby enabling the company to compete with most other companies while retaining its margins. As a reminder, Lantus patents begin to expire in Europe in 2014 and in the US in 2015.

Questions and Answers

Q: Can you provide us with an update on the iBGStar and BGStar glucose meters? Do you expect the meters to have a big impact on the company this upcoming year?

A: Well, these meters are certainly innovative models, but we will have to wait and see. Right now, there are no meters that patients find really useful. Approximately 80% of meter use is intended to help calculate the needed dose of insulin by the patient, but meters cannot do this currently. So we first got interested in blood glucose meters because we thought that products with greater accuracy that would also allow patients to easily calculate insulin doses would increase insulin adherence and improve sales of Lantus. The BGStar looks like other models of meters more or less, but has some innovation. The iBGStar, on the other and, is shaped like a little nugget. It plugs into an iPhone or iPod and can turn those two Apple products into blood glucose meters. Importantly, the iBGStar will allow an individual to calculate doses of insulin needed based on blood glucose readings and will be able to store blood glucose readings so that physicians and patients can look at trends over time. Other iPhone or iPod applications can also be used along with iBGStar to help people understand the progression of their disease and improve their self- management. For example, applications may allow you to count calories and carbohydrates consumed during a meal. The device is also very accurate at **15**%. In actuality, accuracy may be even better than this at **10**%. In terms of our business however, it remains the case that we plan to use these meters to help drive more Lantus sales. It remains to be seen how much we can really compete with other blood glucose meter companies. The iBGStar will be sold in Apple stores, so as you can see, we are employing a consumer-targeted commercialization model. Looking forward, I can even see an application of this type of mobile technology well beyond diabetes. Everyone carries a cell phone, so cell phone based health solutions provide a convenient way in which health care providers can remain in contact with patients and health care can be improved. So in the back of my mind, I am thinking about how we could exploit this technology for other disease areas and develop better health cares outcomes.

Q: Could you expand on your hopes for the use of such a technology outside of the diabetes space?

A: It wouldn't necessarily involve monitoring, but could be behavioral or motivational in nature. Have you ever talked to a cancer patient? It is a complete nightmare to figure out how to deal with cancer. How do you learn how to live with the disease? How do you adapt? One way in which we can help patients is by providing them with a different type of service than just a pill. We know that almost everyone has a cell phone; we all consult our cell phones constantly. So, why not use cell phones for health care purposes by finding ways to use provide mobile educational, motivational, and communication services**.**

Q: With the recent deal between Pfizer and Biocon over the development of biosimilar insulin products, does sanofi have a concrete plan of launching biosimilar products itself?

A: Well, we are already selling Lantus pretty much everywhere in the world. Plus, Lantus is doing very well against biosimilar products (including Biocon's) in India currently. Outside of emerging markets, it remains to be seen what regulatory pathways will turn out to be for biosimilar compounds. Furthermore, companies hoping to produce biosimilar products will have to deal with elements of capacity, compatible devices, and quality. It won't be that easy for biosimilars to gain approval and begin cutting into the market share of current patent protected insulin products. Our goal is to develop a whole range of diabetes products, not just insulin. That's why blood glucose meters and our GLP-1 agonist are important to us. We want to grow our business so biosimilars will not pose that much of a threat. As we've stated before, we do no believe that the patent cliffs for insulins will be typical. But we are not taking any chances. We have a new Lantus plant being constructed in China. This is important because if you have local manufacturing capabilities, you can manufacture at a local price and can compete with anyone. This is a great advantage that sanofi has over others that have outsourced their manufacturing.

Q: What are some of your growth plans for your various businesses?

A: I think that for all the businesses that we have, we will have to develop a critical mass so that we can be number one, two, or three in each particular space. If we can find acquisitions that will add value, we will go ahead and acquire those assets so that we can we grow the business to achieve a critical mass. If we are unable

to find ways to build toward a critical mass, then we should be questioning whether we should really be keeping it. With our generic business for example, we had about 30 million Euros in sales several years ago. Then, we bought Medley and Zentiva, which has allowed us to develop a pretty broad generic market that covers most of the globe other than Western Europe and the US (regions we really don't want to be in anyway). Now we are major players in the generic market.

Q: You mentioned that you will be taking a radical look at research. How about development?

A: We actually have done quite a lot on development. I am pretty comfortable with where we are at on development. I believe that we execute quite well on clinical trials. Research is something different. I think the entire science community has gone down the wrong path. Just because something works in a mouse doesn't give you proof of concept. However, many in the scientific community are excited by mouse data. The mouse market is pretty limited. Industry as a whole is spending tens of billions of dollars on research and development each year, but in comparison, the number of actual drugs approved by the FDA is very small relatively. This is not a productive use of research and development expenditures. We'll give you more color on this later.

SANGAMO BIOSCIENCES

Edward Lanphier (President and CEO, Sangamo, Richmond, CA)

In one of the final presentations of the conference, President and CEO Edward Lanphier provided an intriguing overview of Sangamo's zinc finger protein technology platform and the company's diabetic neuropathy candidate SB-509. The company's novel platform is based on the engineering of zinc finger transcription factors (see below) to create therapeutics, which have the ability to modify, delete, or regulate the transcription of specific genes involved in disease pathology. SB-509 is Sangamo's lead compound under investigation as a treatment for diabetic neuropathy and ALS in phase 2 studies. The compound works to activate the transcription of VEGF-A, an important growth factor implicated in both neurogenesis and angiogenesis. Lanphier emphasized that SB-509 represents a "first-in-class, disease modifying drug" for the treatment of diabetic neuropathy - unlike current diabetic neuropathy therapies (which only address the symptoms of the condition), SB-509 promotes nerve regeneration and has the potential to halt and reverse the progression of further nerve loss. Thus far, SB-509 has shown promise as a nerve regenerative therapy in both a phase 1 and phase 2a trial in individuals with type 1 and type 2 diabetes. The candidate drug has been safe and has been able to lead to statistically and/or clinically significant improvements in several measures of nerve function and nerve regeneration including NIS-LL, IENFD, NCV, and QST (described below). Notably, Lanphier stated that all of these endpoints are considered to be approvable endpoints by the FDA. A phase 2b trial (trial 901) examining the safety and efficacy of SB-509 in individuals with moderate severity diabetic neuropathy finished enrollment last month and results are expected in 2H11. If results are positive, it was made clear that the company will look to partner SB-509 before initiating a phase 3 program. In our view, given the significant unmet need, novel pharmacology of SB-509, and positive results observed in early trials, we believe SB-509 holds promise, and we look forward to hearing the phase 2b results later this year.

- **Lanphier provided an overview of Sangamo's zinc finger protein technology platform.** The technology is based on the engineering of a common class of human transcription factors called zinc finger proteins (ZFPs). ZFPs are composed of two different domains: a DNA recognition/ binding domain and a functional domain that can usually activate or repress gene transcription. By altering the DNA recognition domain and attaching a particular functional domain (i.e., transcription activator, transcription repressor, endonuclease), Sangamo is able to develop therapeutics that can regulate or modify specific genes involved in a disease's pathology. SB-509 is Sangamo's lead compound, and it acts as a transcriptional activator of VEGF-A, which has been demonstrated to play an important role in both angiogenesis and neurogenesis. It is currently under development as a treatment for diabetic neuropathy (phase 2), ALS (phase 2), Parkinson's disease (preclinical), spinal cord injury (preclinical), and stroke (preclinical).

- **Lanphier emphasized that unlike current therapies for diabetic neuropathy, SB-509 addresses the underlying cause of the condition and acts to halt or reverse nerve loss.** Results from a phase 1 and phase 2a trial have been promising. Thus far, the company has been able to show significant improvements on several measures that suggest a neuroregenerative effect of SB-509 in individuals with diabetic neuropathy including improvements in intraepidermal nerve fiber density (IENFD, a histological measure of nerve fiber density in the skin), NIS-LL (a neurologic exam scale for diabetic neuropathy that involves muscle, sensory, and reflex testing), nerve conduction velocity (NCV), and QST (a measure of vibratory sensory perception threshold). Additionally, Lanphier indicated that Sangamo has identified individuals with moderate severity diabetic neuropathy as the best responders to treatment with SB-509 through these trials.
- **A phase 2b trial examining the efficacy and safety of SB-509 in individuals with both type 1 and type 2 diabetes with moderate severity diabetic neuropathy completed enrollment in December 2010 (n=170).** Individuals were randomized to receive either SB- 509 or placebo. For those randomized to receive SB-509, 30 mg will be administered through 22 intramuscular injections in each leg with a 25-gauge needle. According to management, the procedure takes approximately an hour to complete. Dosing will take place on three occasions: on day 0, 60, and 120. While the number of intramuscular injections required for this procedure maybe viewed as a limitation of the treatment, we note that those who elect to receive this treatment will likely be among the more motivated of individuals with diabetes. Furthermore, we view the two-month duration between treatments as a significant plus. Efficacy will be measured by several endpoints including IENFD, NIS-LL, sural nerve conduction velocity, and QST (measure of vibratory sensory perception threshold). Importantly, it was repeatedly stressed during today's presentation that these endpoints are considered approvable endpoints by the FDA. Results are expected from this trial in 2H11.

Questions and Answers

Q: In your diabetic neuropathy studies, are you seeing any restoration of sensory function?

A: In short, yes. To assess restoration of sensory function, we used two measures: 1) quantitative sensory testing (changes in vibration sensitivity from baseline), and 2) the pin prick component of the NIS-LL. In our 701-B trial in patients with severe diabetic neuropathy, people who lacked sensitivity at baseline improved the most, whereas those who were more sensitive to the pin prick at baseline improved less.

We've presented here for a number of years now. The science that we do is proprietary - we're not just another small molecule or antibody company. As much as we try to educate people about our technology platform, we understand that it takes awhile for people to let this percolate long enough to get it. Two things in recent times have brought more attention to our program - the increasing visibility of our clinical program, and our partnership with Sigma-Aldrich. The royalties we have received from Sigma- Aldrich show that pretty many of the major companies in the area are now using our technology to create transgenic rat models, engineered cell lines, etc. There has been an upward bubbling that this stuff works, and it's amazing. With our technology, we can create transgenic rats with any targets you want. It's never been done before. It's finally percolating upwards with our advancement of clinical trials that demonstrated putative efficacy.

Q: When do you anticipate going cash flow positive?

A: I think the official answer is that we don't give guidance in terms of those kinds of data points. But as I think you know, we've been quite prudent in terms of cash use. Going forward, it will be important for us to get a better understanding of the royalty stream from Sigma-Aldrich and Dow as the products we have developed with them become more mature. We'll let them speak to that, and we will not give any individual guidance. As a company, hopefully we'll be cash flow positive in a reasonable time frame. A lot of that will depend on partnering and how many of these future trials they will pick up to reduce our burn rate.

If we are successful in our trials, our near-term business model in the next two to four years is to focus on our SB-509 asset. We want to take it forward to a point of clear value inflection by derisking it from safety and efficacy concerns, and establishing the ability to move forward with approvable endpoints. Partnering would

provide meaningful financial opportunities for us, and it would take off some of the burn of pivotal trials and so forth. Ultimately, we would like to innovate further with our unique technology platform, which is agnostic to the target. It can be used to target many diseases. Driving changes at the DNA level is much different than what is currently being done.

Q: Have you had any discussions with the FDA about what the phase 3 trial would look like?

A: We've talked to them a lot about the phase 2b trial. We went over dose, frequency, timing, and endpoints. In doing so, we have a very clear sense of what constitute approvable endpoints in the agency's view.

Q: How many subjects do you intend to enroll in the phase 3 trial?

A: That will largely be determined by the results of the phase 2b trial. From the data, we will determine how many patients we need to enroll in order to drive statistically significant results in the phase 3 trial.

A: To close, I just want to say that the last few years have been a lot about putting ourselves in a position to have phase 2b data out this year for SB509, and to have human data for our HIV drug candidate. I think that the next 18 months are going to be very interesting and I hope they will be positive for our shareholders.

TAKEDA

Yasuchika Hasegawa (President and CEO, Takeda, Tokyo, Japan)

Takeda President and CEO Yasuchika Hasegawa outlined the company's strategy to minimize the negative financial impacts of the upcoming trough by mitigating the impact of patent expiries, continuing to drive innovation, and achieving globalization. Consistent with prior financial updates, Hasegawa noted that Takeda hopes to submit its DPP-4 inhibitor alogliptin (currently marketed as Nesina in Japan) to the FDA in 2011, and is currently conducting the EXAMINE cardiovascular outcomes trial in the US (please see November 8, 2010 Closer Look*). In addition, Hasegawa expressed confidence for Contrave, which has its PDUFA date set for January 31, 2011. Notably, during discussions we had with Takeda's global head of development after the formal Q&A session, she disclosed that Amylin and Takeda are currently conducting studies on new co-formulations of their pramlintide/metreleptin anti-obesity candidate in efforts to develop a twice-daily, or even possibly a once-daily injection, for the combination therapy (four injections per day were used in the previously conducted phase 2 trials).*

- **Takeda plans to mitigate the impact of patent expiries, to continue to drive innovation, and to achieve globalization.** In order to mitigate the impact of patient expiries, the company will aim to drive earnings growth beyond 2013, and to acquire the rights to marketed or near-to-market products. In the metabolic/CV space, Takeda will aim to enrich its product portfolio to increase care for patients with diabetes, including those in emerging markets, and will focus on anti-obesity drugs, in efforts to continue driving innovation. Finally, Takeda hopes to globalize by establishing the appropriate global and regional product mix, expanding its footprint through enhanced M&A and partnering activities, and to ultimately achieve 90% global market coverage encompassing 30 countries. India, Australia, and Russia are the three major countries Takeda plans to enter.

Questions and Answers

Q: Can you talk a little bit more about your presence and sales in emerging markets?

A: As background, the US, Japan, and Europe currently generate approximately 80% of worldwide pharmaceutical sales. However, the remaining 20% will account for 50% of the growth in the industry over the next five to 10 years. That's why emerging markets are critically important. We don't have good coverage in those areas, so we are aggressively expanding our presence. France, Germany, Italy, and the UK are the only four countries in Europe where we have a strong presence. We still need more time to build presence in other countries.

Q: You started operations in Brazil and in Mexico in 2009. What are your plans for the rest of Latin America?

A: Brazil and Mexico are doing well. We have to make a decision on whether operations in Latin America will be possible with our current internal resources, or if we'll need to take more aggressive steps in the M&A area. Brazil is definitely one of the key countries we will be focusing on in the emerging markets.

TEVA

Eyal Desheh (CFO, Teva, Petach Tikva, Israel) and William Marth (President and CEO, Teva North America, North Wales, PA)

During the time allotted for Teva's presentation, Eyal Desheh (CFO) and William Marth (President and CEO, Teva North America) held a question-and-answer session focused largely on the company's generics business and its MS therapies, which include lead product Copaxone (glatiramar acetate) and two late-stage pipeline compounds. In response to a question on the immunomodulatory peptide DiaPep277, currently in phase 3 trials for newly diagnosed type 1 diabetes, management announced they had no updates.

As a reminder, Andromeda bought the (then-phase-2) program from DeveloGen in June 2007 for an undisclosed combination of royalties upon commercialization and "further monetary considerations." In June 2009, Teva paid Andromeda $13.5 million to gain worldwide marketing rights for the compound (then in phase 3). Andromeda remains the sponsor of the three ongoing phase 3 trials listed on clinicaltrials.gov; these are expected to complete in December 2011, December 2013, and March 2014. In July 2010, Evotec bought DeveloGen for $17.9 million, so (according to its website) it is now eligible for the royalties and milestone payments that would have been paid to DeveloGen.

THE ADVISORY BOARD COMPANY

Robert Musslewhite (CEO, The Advisory Board Company, Washington, DC)

The Advisory Board Company is a leading provider of information and guidance to hospitals and healthcare providers. The Board aims to improve patient care by dispensing skills and advice to thousands of hospitals across the country. The focus is on affordable care; for example, online tool kits are used to provide updates on healthcare-related news. One of the most interesting parts of the discussion from our view was hearing Musslewhite characterize software tools that access data that allow members to remain competitive by comparing their performance in specific healthcare areas to the performance of other hospitals - we'd love to see some of these diabetes outcomes, even aggregated!

During Q&A, Musslewhite highlighted that the recent healthcare reform bill has benefitted the company because they remain the leading source of advice to providers in "uncharted healthcare territory". He remains optimistic that The Advisory Board Company can stay abreast of the potential changes in healthcare field, and he noted that the growing number of new members (1-2% annually) speaks to the company's trusted knowledge base.

We asked Musslewhite about what advice or programs the company provides to its members about approaching the obesity epidemic and obesity-related diseases. While The Advisory Board Company does not provide hospitals with specific clinical advice regarding the treatment of obesity or associated comorbidites, it suggests principles of how a physician should approach an obese patient, and highlights principles that most effectively serve obese patients. The company regards obesity as a serious chronic disease, and believes the wellness of physicians and healthcare providers is a crucial component of a healthy hospital setting.

We also asked about the company's focus on diabetes and it's approach to advising physicians about patients with diabetes. Musslewhite emphasized that, in the hospital market, diabetes is costly to patients and not very profitable. The challenge lies in managing diabetes without downstream hospitalizations. Therefore, the company hopes that diabetes will lead to new models of delivering primary care and new technological methods of managing care.

VIVUS

Leland Wilson (CEO, Vivus, Mountain View, CA)

CEO of Vivus Leland Wilson introduced Qnexa by stating its "four programs" in development: Qnexa for obesity in the US, Qnexa for obesity in the EU, Qnexa for sleep apnea, and Qnexa for diabetes. As a reminder, the company has scheduled a meeting with FDA later this month to discuss its planned response to the complete response letter. The company is also anticipating a final decision from the EU by December 2011. Wilson also emphasized the importance of the European market, especially highlighting the favorable reimbursement environment compared to the US. Importantly, he noted that the company only plans to launch in the EU once a partner is secured; in the US, the company is preparing to launch Qnexa itself. Furthermore, during Q&A, management indicated that they are not proposing a limited indication with respect to cardiovascular safety concerns. However, also in the Q&A, they mentioned that heart rate tends to only be an issue in patients with higher baseline heart rates; therefore, we wonder whether the agency will be focused on patients with especially high heart rates at baseline. In addition, management emphasized the uncertain relationship between heart rate and cardiovascular risk, especially when this signal is combined with improvements in several other well-established CV risk markers, such as blood pressure.

- **On commercialization plans, Wilson noted that 16,000 physicians account for of all obesity prescriptions and that a layered approach in the top tier primary care sector (based on comorbidity indexes) would result in a call audience of 25,000 physicians that could be covered with 150-200 reps.** With respect to reimbursement, Chief Commercial Officer Michael Miller mentioned that roughly 30% of obesity drugs are reimbursed in the private sector (third-party payers). Finally, regarding pricing of Qnexa, the company still needs to analyze the public policy (government statutes on reimbursing obesity drug treatment), the private payer market, and price sensitivity of the cash pay segment.

Questions and Answers

Q: After your upcoming meeting with the FDA, how will you communicate the outcome to investors? Will it be right after you get minutes to the meeting?

A: Clearly, we'll have the meeting and the minutes will be prepared. We always like to see the minutes first. So, we'll look for that to occur sometime during February, hopefully. If there is something that the FDA wants us to do in terms of re-analysis, we'll do those. We're planning to make the NDA submission after we have answered the FDA's questions. We're optimistically expecting that we'll have a new PDUFA date somewhere around mid-summer.

Q: Can you walk us through the mid-summer assumption?

A: The FDA has two choices - a two-month review or a six-month review. To qualify for a two-month review process, you are required not to submit any new data. We almost qualify because two-year data is a continuation of a previous study, so it is the same patients, just additional data. That said, we realize that this division has more to do than any other division on a per person basis. So I think its reasonable to expect they will take six months from when we re-file the NDA, which would put us at the end of august, under ideal conditions.

Q: Can you give any historical context behind the increase in pulse of 1.6 bpm?

A: The average heart rate increase was 1.6 bpm. There has been a lot of focus on that. We have done outlier analyses and we've looked at a lot of different populations and whether they would be at greater risk. The average baseline heart rate was 70-72 bpm, so a 2 bpm increase doesn't amount to much. It may mean more with a baseline heart rate of 90 bpm. In addition, patients with a higher heart rate at baseline actually saw a decrease in heart rate. The heart rate increases were driven by those with a low heart rate to begin with; low, meaning below 60 bpm.

Q: Sorry, I meant to ask whether the 2 bpm is clinically relevant?

A: In this environment with the Meridia withdrawal - which saw a 4 bpm increase combined with an increase in BP - the committee is doing their due diligence to make sure this change doesn't equate to something unseen throughout the program. Phentermine is obviously driving that small increase.

When you look at predictive models, the Framingham risk score and others, there are several factors built into the risk models. You don't see heart rate built into those models. It has been tested on whether it adds to the effectiveness of the model, but you don't see it; it has not been found to have any predictive value. Blood pressure, however, is in the models and is well vetted.

When you look at heart rate in isolation, you need to look at it in the context of the clinician. It's very important to remember that in our program, the 1.6 bpm mean increase in heart rate was associated with significant reductions in diastolic blood pressure and systolic blood pressure. The historical literature doesn't do a good job of teasing out individual markets. So when you do a univariate analysis, you see a relationship, but when you do a multivariate relationship, it's hard to tease out individual factors.

Q: Can you put this in perspective and what the increase of blood pressure means?

A: I want to be very clear about this. There is no blood pressure increase associated with Qnexa. We're seeing significant reductions in blood pressure in patients treated with Qnexa and it's statistically significantly different compared to placebo. There is a greater degree of blood pressure reduction in those with hypertension. Again, risk from blood pressure increases has been well quantified. Every 1 mm Hg increase in blood pressure is associated with an increased risk.

In addition, the reductions in blood pressure were dramatic and occurred very quickly. There is a mild diuretic effect. One thing to clarify though is that our complete response letter did not talk about blood pressure at all. There was no blood pressure question to address in our CRL. That said, all the data on blood pressure, starting with the first time point, says that it goes down and stays at a point that shows significant reduction.

Q: Do any products on the market have a similar effect of increasing heart rate while decreasing blood pressure?

A: Vasodilators can do that for a short time.

Q: After the last panel on one of your competitors, do you have a good feeling that the cardiac worries can be addressed in a post-approval trial? Also on teratogenicity, the FDA can institute a REMS program. Some of these can kill a program.

A: Relative to CV effects, we remain confident that we don't have any issue that would necessitate a pre-approval CV outcomes study. Because every surrogate we've measured improves - lipids, glycemia, etc. - the minor increase in heart rate is the only surrogate that gives any indication whatsoever. So we're very interested in an outcomes study and we think it would be favorable for us.

On REMS, when we initially submitted the NDA in December 2010, the initial REMS program looked very similar to what topiramate has. That's what went into the initial NDA. After the advisory panel, we updated information based on discussions at the advisory panel and submitted a more robust program, and had some discussions around that. The CRL asks to see that in detail as part of our CRL submission. That's the work we've done. Our goal is to make sure there is appropriate communication, appropriately trained physicians, appropriately selected patients, and the understanding that any weight loss therapy should not be used if you are planning to become pregnant or are pregnant. There will be a description of the risks as they're known. Regarding our work around teratogenicity, we feel that it's not supportive of significant risk and there is category C on currently approved products. That will be part of our discussions later this month. We want the drug to be used appropriately by the right patients.

People ask if we're expecting a retinoic acid type of REMS. Let's look at retinoic acid. The incidence rate of major malformations with this agent is 20-30%. It's a known teratogen. Compare that to topiramate, which has been on the market for 15 years with a registry for teratogenicity and there has been no signal for doses even above 400 mg. There is no signal from all of the registries around the world that says this is a teratogen. This is largely a carry-over from early anti-epileptic drugs that were teratogenic. So are we expecting a retinoic acid kind of REMS? No way. Do we think REMS will restrain sales significantly? No.

Q: What kind of patient population do you plan to monitor in your REMS program?

A: We've focused our discussion on teratogenicity. The REMS is designed to assess risk across the entire program. It is designed to look at anything of risk described in the labeling. We've spoken just about the teratogenicity side, but our expected label will be as the indication is stated in the guidelines: men and women, with a BMI greater than 30 or 27 with comorbidities. We expect women with child bearing potential to be counseled to use the appropriate birth control.

Q: What about the CV concerns?

A: We're not expecting the indication to be limited. We're expecting to include it as part of the REMS and the communication plan. We will educate the physicians on the known risks and potential risks.

Q: So if I am a physician, how would I evaluate the risks of Qnexa?

A: You start with label. It's the package insert that comes attached with the drug. It will be on the website, in the Dear HCP letter, and the medication guide. These are the elements when you launch a new drug to make patients and physicians aware.

Q: Why do you think the last panel came down so differently?

A: I think everyone in this room has an opinion. I would boil it down to the evolution of the FDA and the medical community and about the seriousness of obesity and having drug approved for obesity. The first two panels came under considerable criticism for lots of reasons. The last panel didn't follow two days of discussions on Avandia. I'm a CEO and I look at the bright side always. I think we got the results we wanted out of all three panels individually - you have wins along the way. We never believed a pre- approval outcomes study would be required. I do think that the FDA takes it into totality. I think it has been a very useful process although certainly it has aged me quite a bit. I've been doing regulatory work for 30 years and they generally get it right, so I'm very confident they will get it right.

Also, just to mention, during that time frame, Meridia was pulled off market, and the LAP-BAND was evaluated in its own advisory committee to receive a lower BMI indication.

Q: You mentioned a key word, "sales." Lets assume you get approval, what are your plans for timing and selling the product?

A: In the US, right now I would characterize the obesity market as underdeveloped. There is a low treatment rate and they are not largely paid for, but we have an opportunity to build on that. When you look at prescribing, there are 16,000 physicians that account for of all obesity writing. If you layered in your top tier primary care based on comorbidity indexes, you get a call audience of 25,000 physicians, which can be covered with 150-200 reps. We're going forward with the plan that we'll be launching in the US ourselves and so we'll be preparing as such. In EU, we would seek a partner.

Q: Given the lack of managed care coverage, how do you think about a price point?

A: I would say that I see it as an evolutionary process. I think payers will get there. There are very progressive employers that that pay the prescriber and about 1/3 of obesity drugs are covered by third pay party payers. When you look at pricing, you need to look at the balance of what the out-of-pocket cost would be and the sensitivity around that. Moving forward, we need to look at public policy around government statutes of obesity drug treatment, payer situations (on which a pharmacoeconomic paper should be out soon) and sensitivity of the cash pay portion of the market.

Q: Do any states or Medicaid programs pay for these?

A: No.

Q: On efficacy, there is clearly a lot of flexibility in the dosing. How do we deal with the incentive to construct Qnexa from the two generic components?

A: Our lineage is Alza, the godfather of how you take a generic drug and prevent substitution. There are numerous reasons why we believe generic substitution will occur at a low rate. First, the doses we use are not used in the marketplace. So, there cannot be any pharmacy substitution. Secondly, we have improved the side effect profile by having a controlled release formulation, specifically on topiramate. And there are many other

reasons. The challenge in the obesity market for the writing physician is that the history of lawsuits is so powerful that a physician, in my opinion, would have a very difficult time writing generics with different PK profiles and side effect profiles, etc. We have talked to a number of payers who will not substitute because of liability issues.

This is an example of where REMS can actually be an ally. REMS was mentioned as a bad thing before, but it can be a good thing in this regard, if patients are obligated to get a medication guide on every dispensation that has to be done. So if pharmacies were to dispense the drug without giving a proper medication guide, it's not following the REMS.

WEIGHT WATCHERS

David Kirchhoff (CEO, Weight Watchers, New York, NY)

Weight Watchers CEO Davis Kirchhoff opened this presentation by focusing on the recent increase of obesity domestically and abroad (Europe and Asia) and the company's preventative measures to decrease the prevalence of obesity, type 2 diabetes, and other cardiovascular risks. Kirchhoff explained that obesity and its associated diseases not only cost the US $200 billion per year-9% of total healthcare expenditure-- but also are time bombs in which a large population of patients faces increasingly severe and costly diseases. Kirchhoff explained that although long-term behavior change is extremely challenging to impact on a large scale, Weight Watchers focuses on lifestyle change and behavior modification to combat obesity. The company believes that its integrative, convenient, and affordable approach provides the tools necessary to create sustainable behavior change. Weight Watchers has physical meeting locations, traveling meetings, and an online education, nutrition, and exercise program. The company aims to achieve a 10% weight loss in its obese clients, reducing the chance of developing type 2 diabetes by 50%. Many Weight Watchers clients either already have type 2 diabetes or pre-diabetes. The company provides unique guidance but no specialized program for these patients. Moreover, Weight Watchers is dedicated to clinical research to prove the efficacy of their program. A randomized control trial done in the UK found that Weight Watchers participants lost twice as much weight as those given weight management advice from their physicians. The cost of the Weight Watchers program, approximately $1000 per patient, is also much less expensive than other obesity treatments such as bariatric surgery or drugs. Kirchhoff expressed interest in future partnerships, such as a joint effort with a smoking cessation program, but he clearly stated that Weight Watchers would not partner with an obesity drug. Rather, Weight Watcher's distinction is that it provides a safe, "no shame" environment of overcoming the challenges of maintaining a healthy lifestyle. Overall, the Weight Watchers presentation provided us with a unique perspective on positive lifestyle changes that can successfully and affordably prevent and decrease the prevalence of obesity and type 2 diabetes in the US and abroad.

Panel Discussion

CHINA HEALTHCARE MARKET OPERATING ENVIRONMENT PANEL

There was a China "track" at the JP Morgan conference this year that was crazy busy and had a lot of interest. A panel convened Wednesday emphasized that the China market has unparalled potential for development. Panelists identified the challenge of conflicting interests between multinational and local organizations: while the multinational companies were said to look for shorter-term, one-product collaborations and immediate benefits (we found this assessment surprising), the local Chinese companies aim for long-term effects and to change healthcare more broadly speaking. The panel speculated that the next phase of partnerships would involve market access and penetration, marketing not only to urban but also rural areas, and addressing greater unmet needs (liver disease, gastric cancer, and other illnesses that plague both the East and West). They also identified the challenge of finding the most suitable local partner, given the large number of organizations and the different characteristics among them. In addition, they noted that multinational firms must understand the risk involved in working with local organizations. In turn, such organizations may sacrifice global collaboration to focus on strengthening their own foundations.

LUNCHEON KEYNOTE ADDRESS: JAMIE DIMON

Jamie Dimon (CEO, JP Morgan Chase, New York, NY)

During a luncheon on Tuesday, Jamie Dimon spoke with a (to our ear, surprisingly) optimistic tone about the future of our economy, predicting that jobs will increase and the housing market will improvewithin the next few years. With respect to housing, he cited the recent increase in renting as a predictor for a future increase in house sales. Dimon spoke with a tone of disappointment with respect to US immigration policies, noting that we are losing many US-educated young people who are not allowed to become citizens after their education. He added that, sadly, these young people take their excellent training out of the country. Other highlights of Dimon's speech include his prediction, ("with 70%-80% certainty"), that the Euro will not fail and overall optimism about healthcare reform. Overall, his speech was captivating, animated, and candid.

-- by Ben Kozak, Joe Shivers, Sanjay Trehan, Vincent Wu, Maggie Huang, Alice Woolverton, and Kelly Close