Closer Look

JP Morgan Healthcare Conference

January 13-16, 2014; San Francisco, CA; Day #3 Top Ten Highlights - Draft

Executive Highlights

Hello from San Francisco, where we are becoming increasingly deft at squeezing through the jam packed Westin St. Francis in order to get between JP Morgan presentations and breakouts - the crowds also got a bit easier to navigate today! New clinical data from Lexicon's first-in-class SGLT-1/SGLT-2 dual inhibitor LX4211 represented a major highlight of the day. In a phase 2 trial in type 2 diabetes patients with renal impairment, the drug led to substantial (50-60 mg/dl) reductions in postprandial glucose in both the moderate and severe renal impairment subgroups. Efficacy in patients with renal impairment could well be a major differentiating factor against the growing field of selective SGLT-2 inhibitors. Data from the open-label pioneer phase of a very small phase 2 study (n=3) in type 1 diabetes patients demonstrated 20-80% reductions in bolus insulin requirements along with modest weight, fasting glucose, and hypoglycemia benefits. Management stated that data from the expansion phase of an exciting phase 2 study of LX4211 in type 1 diabetes should be available in March.

In technology, the major highlight came from Valeritas, who announced its intention to go public in the second half of 2014! The company saw 13,500 prescriptions for the V-Go insulin delivery device in 4Q13, a ~10% increase year-over-year in what many would call a new market. Gains in reimbursement have come as well, as 55% of patients are now said to have formulary access to the device. Tandem just went public in November, signaling significant investor interest and anticipation for the company. Also in insulin delivery, Insulet CEO Mr. Duane DeSisto discussed the strong performance of the OmniPod, highlighting the company's impressive pediatric base, potential for growth, differentiated position, and exciting platform opportunities (U500 insulin, CGM integration, other drug delivery). The focus this year is on "execution" and driving sales of the new pod - the addition of 20 new sales reps should help quite a bit in this regard. Notably, we heard that sales reps are making 50% more this year with the new pod (given more commission). The Insulet presentation was full of gems on the state of the pump field, the competitive landscape, and updates on the integrated CGM front. Meanwhile, BD CEO Mr. Vincent Forlenza updated attendees on its intriguing pipeline, noting that the company's insulin infusion sets (in partnership with JDRF) will likely be launched in a little over a year. BD also expressed confidence in its CGM program (supported by JDRF/Helmsley Charitable Trust), with data expected to readout early next year and the study wrapping up this fall. Mr. Forlenza cautioned that the device is a "few years away," which certainly presents a strategic challenge for BD - by that time, it will be interesting to see what the field looks like, especially with such robust pipelines from Medtronic, Dexcom, and Abbott. We were surprised to hear Mr. Forlenza mention that the company is looking internally into patch pumps for MDI users - but certainly BD knows that insulin delivery continues to be a major challenge and we salute the company for wanting a place in every delivery option.

On the pharma front, MannKind CEO Mr. Al Mann spoke at "the crack of dawn" on the regulatory and partnership status of Afrezza. The drug has an advisory committee on April 1 and a PDUFA date just two weeks later. While technically a partnership could come pre- or post-approval at this point, we would think at least from a valuation perspective, there is slim to no chance it will come pre-approval. MannKind said parties are not concerned about the approvability of Afrezza, but rather, what the label will ultimately look like. This was a truly standout Q&A with Mr. Mann unscripted on FDA, partnering, and a basal-only pump combined with Afrezza. We would think in the era of degludec (Novo Nordisk), there would still be concern about FDA and related unpredictability.

On the obesity front, Vivus announced that 124,000 scripts for Qsymia (phentermine/ topiramate) were written in 4Q13, up 14% sequentially from 3Q13. Looking to the future, Zafgen positioned its phase 2

injectable beloranib (a MetAP2 inhibitor) for "severe obesity," suggesting that with 12-week weight loss of ~7-11% beloranib could be a "serious alternative" to gastric banding. Additionally, Zafgen's pipeline now includes two preclinical MetAP2 inhibitors: one for the treatment of general obesity, and another for nonalcoholic steatohepatitis.

In the conference's largest ballroom Aetna CEO Mr. Mark Bertolini described his vision for role of payers in a post-ACA America, and how (at least Aetna) will likely make money doing it. We also attended presentations from Connexio Life Sciences, Express Scripts, Genfit, JHL Biotech, MicroPort Scientific, Sinopharm Group, Resverlogix, Rite Aid, Walgreens, and Weight Watchers; however, these sessions did not feature major diabetes or obesity updates. Our full report of the JP Morgan Healthcare Conference will include our coverage of these companies' presentations.

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Top 10 Highlights

1) Lexicon CEO Dr. Arthur Sands (who we recently learned will be departing the company) shared exciting new data on the SGLT-1/SGLT-2 dual inhibitor LX4211. His presentation showcased full results from a phase 2 study of LX4211 in 30 type 2 diabetes patients with moderate or severe renal impairment (eGFR of <60 ml/min/1.73m² and <45 ml/min/1.73m², respectively). After one week, patients on LX4211 saw a 50-60 mg/dl reduction in postprandial glucose compared to baseline. Notably, this difference was preserved in the patient subgroup with severe renal impairment (efficacy is usually reduced in patients with severe renal impairment with selective SGLT-2 inhibitors). Dr. Sands also re-presented promising data from the open-label pioneer phase (n=3) of a phase 2 study investigating LX4211 in type 1 diabetes patients, and stated that data from the larger placebo-controlled expansion phase should be available in March (we heard this data at ADA; The drug led to a substantial (20-80%) reduction in the three patients' bolus insulin requirements, and seemed to have modest FPG, weight, and hypoglycemia benefits). We heard little on the company's "refocusing" away from discovery-stage research and towards LX4211's commercialization. Partnerships discussions for LX4211, which have drawn on for well over a year, are still in progress according to management; we assume that the restructuring will enable the company to be without a partner longer, until it can draw up the optimal partnerships. See our Lexicon 3Q13 Report for the company's previous guidance and thoughts on LX4211, as well as pages 7-9 of our EASD 2013 SGLT-2 Inhibitor Report for promising gastrointestinal and genitourinary data we saw on the candidate.

2) Excitingly, Valeritas announced that it aims to go public in the second half of 2014. The V-Go launched regionally in the US in April 2012, expanding the sales region near the beginning of 1Q13 and again around mid-year 2013. In 4Q13, ~13,500 prescriptions were written for the V-Go, up ~9% year-over-year. (For context, Tandem went public on November 13, 2013 having sold 3,200 pumps as of June 30). Since the V-Go's launch 21 months ago, over five million devices have been produced (24-hour wear). CEO Ms. Kristine Peterson highlighted that the company has "de-risked manufacturing" and transitioned to a high-volume source of supply based in China, both important for expanding access and reducing the cost of the device. The V-Go has also gained reimbursement both commercially as well as part of Medicare Part D (over 55% of people have formulary access, and those who don't have formulary access gain V-Go through medical exception). This is certainly key in this healthcare environment, particularly for type 2s who have lots of other co-morbid healthcare expenses. Additionally, CEO Ms. Kristine Peterson remarked that the company is looking into partnerships in both the US and abroad, although this wouldn't happen until at least 2015.

3) BD's Q&A was packed with info on its diabetes business, with CEO Mr. Vincent Forlenza discussing insulin infusion sets, CGM, and, surprisingly, a potential venture into the patch pump market. First discussing the infusion sets, Mr. Forlenza characterized three issues with current offerings: 1) tube kinking; 2) insulin crystallization (and a subsequent drop in insulin flow rate); and 3) the difficulty of insertion. BD believes that it can improve on these issues by applying learnings from its acute care catheter technologies business. Mr. Forlenza characterized the infusion set products as "slightly over a year away." Although BD is capable of going to market on its own, Mr. Forlenza also remarked that the company is open to partnering (e.g., with existing pump manufacturers). Turning to the development of BD's optically-based CGM (funded by a JDRF-Helmsley Charitable Trust collaboration announced at ADA 2012), Mr. Forlenza remarked that there has been some "very good early data" - the device is accurate, has limited drift over time, reduced calibration, and reduced warm-up time. The company is "miniaturizing" the product and collecting more data at this time, with results expected to read out in early 2015 (the study will complete this fall). Although Mr. Forlenza acknowledged that that CGM market is becoming increasingly competitive with next-gen products, he believes that BD's CGM still has a niche. The timing on this product continues to get stretched out ("we're a few years out"), meaning the competition from Dexcom and Medtronic will be that much more intense once it launches. (As a reminder, JDRF is also funding the development of a combined insulin infusion set/CGM, though this was not discussed.) Notably, Mr. Forlenza spoke about insulin pumps; while BD has "no interest" venturing into the higher-end pump market (i.e., Animas and Medtronic), the company is interested in smaller, patch pumps that specifically target MDI users. He highlighted that the company is "investing in technology internally." We will be interested to see if BD commits to this area, and if so, how it will differentiate itself from Insulet's OmniPod, Valeritas' V-Go, CeQur's PaQ, and others in development. Mr. Forlenza did not discuss Biodel's F4Q13 acquisition of exclusive rights to BD's Uniject device for a liquid stabilized glucagon.

4) Insulet CEO Mr. Duane DeSisto discussed the latest on the OmniPod, focusing on key customer demographics (70% of OmniPod customers are new to pumping), strong sales growth (30% year-over-year), and the product's unique position as the only tubeless insulin pump available. Insulet's installed base is ~60,000 customers now, representing ~15% of the US insulin pump market - for context, that's 33% growth from 45,000 customers and ~10% of the market one year ago. Mr. DeSisto emphasized that this year is "all about execution" and driving sales of the new pod, unlike past years that have focused on manufacturing or getting products through the FDA. Management reiterated remarks from the 3Q13 call that Insulet will hire 20 new sales reps. On the pipeline side, we learned that Insulet is in the process of converting the OmniPod handheld for compatibility with Lilly's U500 insulin; the goal is to have a submission in by the end of 2014 and to start clinical work next year with Lilly. Regarding the CGM-integrated pod, Insulet and its unnamed private partner have a solution to the sterilization issue. R&D will now focus on the insertion and sensor configuration, followed by animal studies. The hope is to "take a hard look" at starting human studies by the end of 2014. Said management in Q&A, "If I went head to head, it's not as good as Dexcom. But it's not crazy off. We're not trying to replace fingersticks. We want to have a CGM that helps patients stay between the rails. They would set a profile and it would keep them informed." We look forward to seeing more data, since the value proposition of having one item on the body could help get more patients on CGM. Management's comprehensive detail on the business, expectations for 2014, competitive landscape (Medtronic, Tandem, Animas), and Q&A are below.

5) MannKind CEO Mr. Al Mann provided a confident early morning review of the status of Afrezza, the company's inhaled ultra-rapid-acting insulin. The drug was resubmitted to the FDA on October 13, 2013, will have an advisory committee on April 1, 2014, and has a PDUFA date two weeks later on April 15. In Q&A, management said the advisory committee was "sort of expected" given the current regulatory environment. An insightful breakout session discussed the status of partnership talks in some detail - there are several parties at the table, and a deal could come either pre- or post-approval. According to management, those interested in a post-approval deal are not concerned about Afrezza's approvability, but are really waiting to see what the drug's label ultimately looks like (Mr. Mann believes the label will not be as strong as it could be, due to the limitations of clinical trials - more below). In line with previous comments, the preference is a global partner, though MannKind ideally wants to retain co-promotion rights in the US. A partner will ultimately set pricing and launch timing, though MannKind expects comparable pricing to rapid-

acting-insulin analog pens (with perhaps a "single-digit premium") and launch within six months of approval. See below for more detail on this presentation and the outstanding Q&A - Mr. Mann was truly unscripted and gave a lot of color on his view of Afrezza, the market potential, and the possibility of a basal-only pump.

6) In a packed presenation from Vivus's confidence-inspiring new CEO Seth Fischer, the company announced 4Q13 script metrics for Qsymia (phentermine/topiramate). In 4Q13, 124,000 Qsymia scripts were written, up 14% from 3Q13. Since Qsymia's launch in 3Q12, ~35,000 providers have prescribed Qsymia. Of these, ~6,000 prescribed Qsymia for the first time in 4Q13. Unfortunately, Vivus was just under its previously goal of having 50% of commercial lives covered for Qsymia by the end of 2013, although it finished the year with a still very strong ~43% of commercial lives covered. An encouraging note, however, was that CaremarkPCS subsequently added Qsymia to its Performance Drug List and 2014 Prescribing Guide. The new CEO Mr. Fischer seems to have a very good handle on the business and we look forward to hearing more about the company's leadership momentum.

	4Q13	3Q13	2Q13	1Q13	4Q12
Prescriptions	124,000	109,000	81,000	58,962	29,900
Growth From Prior Quarter	14%	35%	37%	97%	-

7) During an early morning session at JPM, private company Zafgen suggested its phase 2 beloranib could be an alternative to gastric banding. CEO Dr. Thomas Hughes suggested that the company's phase 2 beloranib (an injectable MetAP2 inhibitor) could be one of the most potent agents in development for any disease, and a "serious alternative" to Lap Band. For context, in a 12-weeks study mean weight losses of 5.3%, 6.7%, and 10.6% were seen with beloranib 0.6, 1.2, and 2.4 mg, respectively, compared to 0.3% loss with placebo (per-protocol analysis); the main tolerability issue was transient sleep latency during the first month of use (time to sleep increased by 45 minutes). Zafgen has previously stated that it hopes beloranib will confer 20% weight loss. Additionally, Zafgen's pipeline included two notable preclinical additions: an as of yet unnamed second generation MetAP2 inhibitor for general obesity (Zafgen is positioning beloranib for "severe obesity") and ZGN-839 (also a MetAP2 inhibitor) for nonalcoholic steatohepatitis (NASH) and type 2 diabetes. In a rodent model of NASH, ZGN-839 lowered glucose and cholesterol levels while conferring ~5-10% weight loss after 10 days of treatment.

8) Also in the private companies track at JPM, CeQur management highlighted the benefits of patch pumps for people with type 2 diabetes. We were glad to see that CeQur' PaQ and Valeritas' V-Go were highlighted in *Diabetes Forecast's* Top Tech on the Horizon 2014 - great recognition of novel insulin delivery devices alongside products like WellDoc's BlueStar and Abbott's Flash Glucose Monitoring. We received a refresher on the company's previously presented data (ADA 2013) that demonstrated decreased A1c and insulin requirements for patients using the PaQ insulin delivery device. As a reminder, CeQur collected CGM data in this study, something we hope to see a lot more of in the future (particularly in type 2 diabetes trials). In addition to discussing this data, management compared CeQur's PaQ to Valeritas' V-Go and highlighted key points of differentiation: a different number of basal rate options (six for PaQ vs. three for V-Go), different reservoir sizes (330 for PaQ vs. 76 units for V-Go), and different lengths of wear (up to three days for PaQ vs. 24 hours for V-Go). Of course, V-Go is fully disposable and does not have electronics, so the comparison to PaQ, while interesting, is not apples to apples. Given the vast opportunity to improve adherence to insulin and glycemic control in type 2 diabetes, we believe there is significant market potential for both companies' products - we believe the traditional players are also expanding in type 2 and that this won't stop. As with type 1 diabetes, we believe insulin delivery for type 2 diabetes should all be about individualized therapy - products all have pros and cons that will appeal to different patients in different stages of type 2 diabetes with different financial resources, dexterity, and comfort with technology. Said management, "This market is ready; the data is there; the products are ready; and the numbers are going to be big." Not all the products are ready, of course, and reimbursement takes time, but we definitely ultimately agree that better options for taking insulin are a positive for patients and patient families.

9) **It was great to hear from AbbVie CFO Mr. Bill Chase, who reminded attendees that the global phase 3 study of atrasentan for diabetic kidney disease has started.** We took note that atrasentan was the second item listed on the slide entitled, "Strongest late stage pipeline in our history." As a reminder, the compound's phase 3 SONAR trial began in May 2013 (ClinicalTrials.gov Identifier: NCT01858532 and has a primary completion date in February 2017). In line with AbbVie's 3Q13 financial results call, Mr. Chase noted that SONAR would serve as the single global registration trial for the compound. A quick slide on partnership and in-licensing activity caught our attention, as Reata's logo was actually included on the slide but not mentioned. As a reminder, Abbott invested $450 million for rights to Reata's bardoxolone methyl in most international markets, followed by a later investment of $400 million for a follow-up portfolio. Termination of this phase 3 trial was one of our biggest disappointments from 2012; coverage from the terminated phase 3 study were published in November's NEJM - see our coverage here.

10) Aetna CEO Mr. Mark Bertolini shared his vision for the future role of insurance companies - helping health systems manage the financial risk associated with pay-for-performance (by creating co-branded health plan) and empowering patients to make the well-informed decisions about the care they receive (Mr. Bertolini painted a similar picture at the Cleveland Clinic's Medical Innovation Summit). Mr. Bertolini proudly told attendees that KLAS Research (a healthcare IT research firm) ranked Aetna as the most "transformational" payer when compared to Cigna, Humana, and UnitedHealth. Aetna was also characterized as forward thinking by Vivus CEO Mr. Seth Fischer, due in part to the payer's decision to conduct a pilot program to test the benefits (i.e., potential improvement in health outcomes, productivity, and medical costs) of Vivus' Qsymia (phentermine/topiramate) and Arena/Eisai's Belviq (lorcaserin). The pilot will be open to self-insured plan sponsors, and Aetna expects results by the end of 2014. We hope that Aetna will opt to publicize these results so that other payers (and the government) can consider the information when making coverage decisions. Overall, Aetna's business strategies appear to be working - it brought in an expected total of $47 billion in 2013 and aims to have revenue exceeding $100 billion in 2020. We will have more on this and Vivus' very strong presentation today with new CEO Fischer in our company-wide report.

Honorable Mentions

- **Biocon discussed its insulin portfolio in great depth yesterday** (the day's presentations were so good that we had to let one spill over into today's list!). To introduce the segment, COO Dr. Arun Chandavarkar emphasized the need for more affordable diabetes pharmacotherapies in the emerging world. According to his slides, the average person in Africa would need to pay over eight days worth of wages for a month-long course of oral antidiabetic medications, compared to the half day of wages the average European would need to pay for the same drugs. Biocon has seen strong sales growth compared to the major insulin manufacturers; its share of the recombinant human insulin market has grown from 4% in 2009 to 11% in 2013 (in markets where Biocon's product has been available for that timespan). Biocon's biosimilar insulin glargine is registered in "10+" countries, with plans to expand to a broader range of markets in coming years.
- **With lots of talk here at JPM on changing healthcare delivery, we were very impressed to hear Glooko announce last week that it raised $7 million in a Series A-1 round from several new investors.** Newcomers included Samsung Venture Investment Company (SVIC) and Lifeforce Ventures. Other existing investors, including The Social + Capital Partnership, and entrepreneurs Sundeep Madra (of Pivotal), and Yogen Dalal (of the Mayfield Fund), also took part in the fundraising round. Glooko will focus these funds on bringing patient data and decision-making algorithms to health providers and payer groups - that has consistently been identified as a major need and was a clear theme at CES 2014. The investment from SVIC is particularly significant since the company is a leader in the mobile market, providing additional credibility to Glooko's universal data downloading platform (compatible with an impressive 26 glucose meters and 27 mobile devices; both Apple iOS and Android). Glooko's recently launched Android app has already received an update, as statistics are now available - great to see iteration already, a testament to how mHealth can really move at a fast clip. For more on Glooko, please see our coverage of the Android app launch in October and our trip to the company's booth in the AADE Exhibit Hall. For background,

SVIC's major areas of development are semiconductors, telecommunication, software, internet, bioengineering, medical industry, and film/video industry.

Appendix

JP Morgan Healthcare Conference

Insulet

Duane DeSisto (CEO, Insulet, Bedford, MA)

Insulet CEO Mr. Duane DeSisto and CFO Mr. Brian Roberts discussed the latest on the OmniPod this afternoon, focusing on key customer demographics (70% of OmniPod customers are new to pumping), strong sales growth (30% year-over-year growth that will continue into 2014), and the product's unique position as the only tubeless insulin pump available. Insulet's installed base is ~60,000 customers now, representing ~15% of the US insulin pump market - for context, that's 33% growth from 45,000 customers and ~10% of the market one year ago. Mr. DeSisto emphasized that this year is "all about execution" and driving sales of the new pod, unlike past years that have focused on manufacturing or getting products through the FDA. Management reiterated remarks from the 3Q13 call that Insulet will hire 20 new sales reps - coming off the company's annual sales meeting last weekend, it sounds like excitement is pretty high. Apparently the sales force is earning much more than it had been a year ago, when it still had only the traditional pod. On the pipeline side, we learned that Insulet is in the process of converting the OmniPod handheld for compatibility with Lilly's U500 insulin; the goal is to have a submission in by the end of 2014 and to start clinical work next year with Lilly (a valuable update from the 3Q13 call, which said the project was in the "early days"). Regarding the CGM-integrated pod, Insulet and its unnamed private partner have a solution to the sterilization issue. R&D will now focus on the insertion and sensor configuration, followed by animal studies. The hope is to "take a hard look" at starting human studies by the end of 2014. Said management in Q&A, "If I went head to head, it's not as good as Dexcom. But it's not crazy off. We're not trying to replace fingersticks. We want to have a CGM that helps patients stay between the rails. They would set a profile and it would keep them informed." We look forward to seeing more data, since the value proposition of having one item on the body could help get more patients on CGM. That said, we continue to hope that Insulet and Dexcom will resurrect their integration agreement.

- **Management did not release 4Q13 numbers, though mentioned that 2013 sales should fall within the previous revenue guidance of $244-250 for the year (16-18% growth).** The core OmniPod business grew 30% year-over-year in 2013, and the international business grew over 100%. Management reminded attendees that outside the US, the OmniPod has done very well despite competing directly against the Medtronic Veo. Importantly, over 20% of new OmniPod shipments have come from newly prescribing doctors.
- **"We are gaining market share. We are growing the market. If you are a kid on this product, you are never going on a tubed pump."** Management emphasized the encouraging patient demographics that bode well for the business: 70%+ of OmniPod customers are new to pumping (the same stat shared one year ago) and 35%+ of customers are <18 years (up from 30% one year ago - a clear sign of the new pod). Given that 50%+ of people newly diagnosed with type 1 diabetes are <18 years, there is significant upside to expand the business. Said management, "We are incredibly excited about this pediatric population." Insulet has seen 100%+ growth in children <10 years and 60%+ growth in patients <18 years. Attrition is quite low at ~8.5% overall (down from 9% previously), and <5% in patients <18 years.
- **In 2014, the core OmniPod business is expected to grow 30%+ globally, with new patient adds expected to grow 25%+.** This is on par with 2013 performance, where the installed based grew 33% to 60,000 patients. Said Mr. DeSisto, "We finally have some predictability in this business." In line with comments made in the 3Q13 call, Insulet expects to be operating profitable in 2014. No specific revenue guidance was given for 2014, though management "would be disappointed" if total revenue did not exceed $300 million (~21% growth).

    - **Insulet estimates that 27% of people with type 1 diabetes in the US are on insulin pumps** (405,000/1.5 million patients), expected to rise to 50% penetration (900,000 patients/1.8 million patients) by 2018. This assumes 3% compound annual growth for patients and 10% compound annual growth for pumps. These same stats were shared at JPM 2013.

- **Management commented that Medtronic "has had trouble" with the launch of the MiniMed 530G based on what it knew about the launch** (some through distributor Neighborhood). Since the FDA approved the Minimed 530G as a pump-CGM system, Medtronic cannot sell the components individually. This requires patients to obtain separate prescriptions for the CGM and pump, which must be secured from a provider and covered by a payer. Said Mr. DeSisto, "Where they've run into trouble with the launch is in trying to convert their installed base." We look forward to hearing how the launch is going when Medtronic reports financial results on February 18.
- **Mr. DeSisto believes that Animas has "completely retracted" and Tandem has scooped up the business.** In Q&A, he highlighted J&J Animas' reorganization, sales force reductions, and a rumor that the business is up for sale. Certainly, J&J had a challenging 3Q13 (sales down 28% in the US), though we assume the company is still very committed to the insulin delivery business.
- **On October 17, Insulet brought on the highly respected Dr. Howard Zisser as the company's first medical director.** Mr. DeSisto explained that Dr. Zisser brings "incredible insight" and a "good patient perspective" for the company's CGM program and a "next-gen handheld." In addition, he believes "that over time, the way companies will survive in the new healthcare environment is "driving outcomes." Dr. Zisser will help with conducting studies to show that the OmniPod can drive better clinical outcomes than MDI and even traditional pumps.
- **Insulet has fielded interest in using its patch pump to deliver an obesity drug that has "pretty dramatic side effects" upon injection** (we wonder if this is Zafgen's beloranib or Novo Nordisk's Victoza). Mr. DeSisto explained the strategic rationale for using the OmniPod to deliver drugs other than insulin: 1) for drugs going off patent, the OmniPod could extend the commercial life by improving efficacy; and 2) to reduce the side effects through basal delivery. Insulet plans to bring on a dedicated business development person to handle the volume of these non-diabetes requests. The company already has an oncology partnership with Amgen (pod only for basal infusion; no handheld required) and a fertility drug partnership with Ferring (a pod and an icon-driven handheld).
- **"The manufacturing piece is the single biggest barrier for anyone trying to do this. It takes a long time to get this right."** In line with recent quarterly calls, Mr. DeSisto reiterated the barriers to entering the patch pump field - Insulet is now making 400,000 (!) OmniPods a month, and the company's goal is to eventually make one million pods a month (and longer term, one million pods a week!). On the IP side, Insulet holds 19 US patents, another key barrier to entry for companies evaluating the field.

Selected Questions and Answers

Q: Touching on the ~40%+ growth in new patients that you had coming out of Q3 - you also indicated that you would end up somewhere in your guidance range for 2013. Did the trend of new patient growth continue into Q4?

A: We feel very comfortable talking about 40% year-on-year growth through 4Q13 for patient starts. So realistically, coming off of all the work of the transition for Q3, I think the momentum we had in the business will continue through Q4. And I think the one thing everyone should keep in mind - as important as the number of new patient starts is, in any given year, 90% of the revenue is coming from re-orders. That's just how the model works. But new patient adds are a lead indicator of better things to come.

Q: People were waiting for the new pod, which disrupted reorder cycles. How will that play into revenue growth in 2014?

A: What we were able to do in 4Q was to renormalize some of those cycles. When we finished 3Q, we had two pods on the shelf. We finished 4Q with a bit of inventory. We had a backlog with Ypsomed and distributors, but got the product back in the hands of the consumers. We have a little catch up here in Q1, and we'll finish that off.

Reorders drive the business in any given period. If you look at it, we're always near the midpoint of ranges. In the first half of 2013, it diverged because reorders were disrupted. People were using up old stock. All of that is past now. By the early part of November, we were done with the installed base transition to the second gen pod. That's all normalized at this point and we're seeing those normal reorder patterns. But Q1 is always the seasonally challenging quarter.

Q: Can you talk about the competition and the dynamics within the pump market?

A: This is probably the first year that there are three new pumps in the market. If you look at it the way we looked at it, Medtronic came out with the 530G and has had trouble with the launch. The FDA approved that product as a pump-CGM system, so they can't break it up. Where they've run into trouble with the launch is in trying to convert their installed base. We've seen this through the Neighborhood Diabetes business. The issue with the installed base was that in order to switch to the 530G, you need a prescription from the doctor. Then you have to go back and get a prescription for the CGM. Some doctors don't have faith in the average Joe Shmo handling a CGM. If a doctor writes a script for both, and the patient goes to the managed care provider, the managed care provider might say, 'I'm not paying for that.' Then it goes back to the patient to pay out of pocket. Medtronic has backed off a little and is now willing to sell the old Paradigm. The initial foray focused on the installed base and not converting MDI patients.

For Tandem, they have this iPhone-type tube pump. I think where they've benefited is it seems Animas has completely retracted. They've shrunk their sales force and moved everything out of California and New Jersey. All the rumors are that the business may be up for sale at some point, so I think there was a vacuum there and Tandem came in. The decision is pretty simple: tubeless or tube. And when you get into tube you play in that space. So I think it's been an interesting year. There is a lot of technology out there. We feel pretty good about where we are. Our reduction in pod size has really attracted this pediatric population to us.

What I'd add is in the tubeless side of the market, I don't think you'll see another entry in the US for another three-plus years. There's Valeritas, which is like a wearable pen, and CeQur is out there banging around, but those are more in the wearable pen-type business and not something we would define as a competitor.

Q: On the CGM side, now that sterilization is fixed, what is next?

A: The next phase is insertion, and we have various iterations. A dual insertion with the insulin and sensor like a snakebite. Another version has one out the back and one out the front. Then we have the bi-lumen catheter, which is what I'm most excited about. We have filed IP around that. The question is if insulin pools up, how do you shut off the CGM? That solution is the easiest, most pain free, most economical way to do it. In the next version, we'll start taking some sensors, putting them in prototype products, testing them on pigs, and evaluating the various iterations. We're excited to have Dr. Zisser with us, since he's given us the pros and cons of all these variations. If that goes well, we'll start building product and trying it on some people. It's still a long way. People ask, 'How good is your CGM? If I went head to head, it's not as good as Dexcom. But it's not crazy off. We're not trying to replace fingersticks. We want to have a CGM that helps patient stay between the rails. They would set a profile and it would keep them informed. How accurate does that have to be for that? Dr. Zisser has seen it all from the early Abbott Navigator to the latest and greatest stuff. Stay tuned. The cool part is that we know the sterilization thing can be done. We spent a lot of time on it and went through lots of iterations.

Q: Up until November when you had your call, it didn't sound like that had been fixed at all right?

A: No, but we've now run four batches of sensors since our last earnings call to really shrink it down. We talked to a group that gave us a couple of ideas that we tried. So if you asked me about making a ten-day sensor, I would say we're miles away. But for four days, what appears to happen is it doesn't seem to affect the

accuracy of the sensor; rather, it just shortens the life of the sensor. But we're throwing the pod out after 80 hours - or at the most extending it to four days. So we're in a pretty good spot either way.

Q: Just a question on inventory build in the quarter - it sounds like you're really where you want to be for manufacturing. But you talked in your Q3 call on building inventory before the Chinese New Year [when factories shut down for two weeks] and for your distributors. How did that play out?

A: In Q3, we built about 1.7 million pods. Here in Q4, we're averaging a bit over 800,000 pods per month, so about 2.5 million pods during Q4. We've had a nearly 50% increase in overall production, which is the benefit of the third line being on for the full third quarter rather than just a few weeks in Q3. That's in really good shape. It's allowed us to keep some of the product we produced at the end of December that we could have shipped to an Ypsomed or other distributor partner to have more stock on their shelves, which they want because the orders are there and open. We made the decision to keep that inventory ourselves. When the Chinese New Year happens and factories close down for two weeks, we will have the buffer to put it where demand is highest. It continues to give us some more flexibility. We have not rebounded our inventory levels where we'd love them to be. But over the course of the next couple of quarters those inventory levels should continue to rebound. Our goal is to get to about 2.5 million in Q1 before the shut down and then hopefully pushing out 3 million in Q2.

MannKind

Al Mann (CEO, MannKind, Valencia, CA)

MannKind CEO Mr. Al Mann provided a confident early morning review of the status of Afrezza, the company's inhaled ultra-rapid-acting insulin. The drug was resubmitted to the FDA on October 13, 2013, will have an advisory committee on April 1, 2014, and has a PDUFA date two weeks later on April 15. Said Mr. Mann, "We've been preparing for it for six to eight weeks. We'll be all ready for it." In Q&A, management said the advisory committee was "sort of expected" given the current regulatory environment - we agree, though would note that this was a departure from previous remarks that Afrezza would NOT have an ad comm. An insightful breakout session discussed the status of partnership talks in some detail - there are several parties at the table, and a deal could come either pre- or post-approval. According to management, those interested in a post-approval deal are not concerned about Afrezza's approvability, but are really waiting to see what the drug's label ultimately looks like (Mr. Mann believes the label will not be as strong as it could be, due to the limitations of clinical trials). In line with previous comments, the preference is a global partner, though MannKind ideally wants to retain co-promotion rights in the US. A partner will ultimately set pricing and launch timing, though MannKind expects comparable pricing to rapid-acting-insulin analog pens (with perhaps a "single-digit premium") and launch within six months of approval. Mr. Mann also briefly reviewed the Afrezza phase 3 results in some detail, highlighting the product's fast PK/PD, weight neutrality, and hypoglycemia advantage in type 1. See below for a truly outstanding Q&A.

- **MannKind expects to have a 375 million Afrezza cartridge capacity at launch, enough to support approximately two million patients.** At full capacity, the Danbury factory could produce up to 2 billion cartridges, though capital expenditures would be required to support this expanded capacity.
- **MannKind has two different cartridge dose sizes for Afrezza in the current FDA filing, though others are in development**. Initially, some percentage of patients requiring larger doses will have to take multiple cartridges at each meal. Ultimately, the goal is to have single dose administration at each meal. Patients would be able to purchase multiple cartridge sizes, though MannKind believes that in most cases this would not be necessary.
- **MannKind had cash of $94 million as of September 30, with cash burn of $10-12 million per month as the company ramps to commercialization.** Subsequent to September 30, the company reported several updates that extend the cash runway: MannKind received $45 million in proceeds from the exercise of warrants issued in an October 2012 public offering; an

additional $40 million from Deerfield in 4Q13; and CEO Mr. Al Mann increased his available borrowings under by $30 million. MannKind has enough financial resources to get through the April 15 PDUFA date, at which point we suspect a partnership might be announced.

- **In Q&A, Mr. Mann discussed his ambition to build a low-cost basal-only insulin pump to complement Afrezza** - this would not be a MannKind program (he has started a group" to look at this), but given his experience at MiniMed, we cannot wait to hear more.
- **"Clinical trials don't show the full benefits of Afrezza."** First, Mr. Mann believes that some patients in the phase 3 trials didn't lower their fasting glucose levels enough to demonstrate larger reductions in A1c. Said Mr. Mann, "As people get more used to Afrezza and start using it more appropriately, you're going to see significant improvements in A1c." Second, some patients may have been accustomed to taking insulin 20-30 minutes *before* meals. If this was done in the Afrezza arm (out of habit and despite the product's ultra-fast PK/PD), hypoglycemia would have been overestimated.
- **Mr. Mann presented data on the number of insulin users in the US, highlighting that ~500,000 patients convert to insulin annually.** The data (a combination of CDC, Roper, and GfK) estimated 6,997,000 insulin-using patients in the US, broken down as follows: type 2 long-acting only (26%), type 2 basal bolus (24%), type 2 premix only (14%), type 2 "other" (not defined; 19%); type 1 MDI (11%); and type 1 pumpers (6%). The slide assumed 22.1 million patients with diabetes in the US, with 57% on orals only, 32% on insulin, 8% on lifestyle, and 3% on orals + GLP-1/GLP-1 only.
    - **Ambitiously, MannKind believes that Afrezza could target a population of over 20 million patients with diabetes in the US**: 4.2 million prandial insulin users, 1.7 million type 2s on basal insulin only, and 15.2 million insulin naïve type 2s who could benefit from using insulin.

Selected Questions and Answers

Q: Why do you think the FDA requested the panel? Or did you expect it all along?

A: We sort of expected it given the current regulatory environment. Also, with the change in EMDAC division, we thought they would probably want one. We started preparing for it six weeks or so ago. We were quite ready for it.

Q: Will it focus on safety?

A: We really don't know at this time. The message was very generic in regards to the rationale for having the advisory committee. Looking at the FDA guidance, we're a first in class, ultra-rapid-acting insulin - it makes sense that they would ask for an advisory committee. We had no lead in terms of any type of focus.

I will say that within MannKind, there is a lot of conversation by people close to program who think this is a real advantage for us. The advisory committee will give us a public forum to communicate the benefits of Afrezza.

Q: The timing of the advisory committee is two weeks before the PDUFA date - is that enough time for the FDA to make a decision?

A: We know from our discussions that the FDA's ambition is to meet the PDUFA date. Two weeks is maybe a little bit on the short side. Usually the FDA doesn't want to have a long time between the advisory panel and the final decision. We are hoping that April 15 is a valid and realistic date.

Q: What is the status of partnership talks? If no partnership is signed, will you launch alone?

A: As we announced, we are working with Greenhill. We are very busy at this point in time channeling this discussion and working on potential. We don't know exactly what the advisory committee and PDUFA date will do to those discussions. But they are checkpoints along the way.

Early on, it had been my ambition to launch ourselves. But then we had the CRL and the extension. I invested $350 million more of my own money, in addition to the $575 million I already invested. That sort of stymied me - I don't have enough personal resources to do an adequate launch myself for the company. So under the circumstances, we are doing a partnership. If I had half a billion to spend, I would do it ourselves.

Q: What partnership deal terms are you looking for? Would you sign a partnership deal before or after approval?

A: We have both groups - partnership deals pre- and post-approval. Some are waiting to see what the label looks like. It's really driven by the term sheets. The only thing we can say is that we'd like to have an opportunity to co-promote in the US.

For the parties that have gone through our program and have done due diligence, they have a comfort level regarding the approvability of the product. Those who are really waiting are not concerned about approval per se, but want to see the label. The initial label is not as strong as it could be. It will show non-inferiority in A1c. As people get used to using Afrezza, it will be superior. We do see some hypos. I don't think the hypos are caused by Afrezza. The hypos caused by prandial doses are because people are taking the dose before they sit down to eat. That's particularly the case in patients with an A1c over 8% who were having hypos - you're not going to get that with Afrezza. Most of the residual hypos are coming from people either taking Afrezza before they are sitting down to eat or other trial factors (e.g., basal insulin).

Q: You have a very interesting delivery system. What other drug candidates do you have beyond the delivery of Afrezza?

A: Lots of them. There is a pain drug that could be effective in a couple minutes instead of 45-60 minutes. Think of Viagra [jokingly] - you could do that very quickly. [Laughter] One of the advantages is we can stabilize large molecules. The reason Afrezza is so effective and quick is we've been able to create a stable formulation of insulin monomers that has never been done before. We can do that for all sorts of drugs. By the way, if you're not taking the dose three times per day, you can use a single-use disposable inhaler. You just use it and throw it away. It only adds a few pennies to the cost of the drug.

We would like to have an improved basal insulin. I think that the best solution would be a basal pump, and I've started a group to develop it. Pump therapy is clearly the best way to deliver basal insulin. I've had a lot of experience in pumps, as you know. I started MiniMed, now Medtronic Diabetes. The fascinating thing about it is even though they do a great job in basal, the kinetics of prandial insulin limit pump performance. Pumps are also very expensive - $7 a day. In type 2 diabetes, you're not going to see insurance companies paying that. I think that can enormously improve to 60-75 cents per day.

Q: In the worst-case scenario where no partner is signed, what would you do?

A: I do believe we will have a partner. We have a number of alternatives. We could go regional - there is lots of regional interest in parts of world. In the US, we could rollout mad start with the high decile physicians or metro areas. That is part of an active contingency plan. But the expectation is we will have a partner. We've had a couple groups approach us and say, 'We will provide the funding for a MannKind-only launch.' But we aren't interested in that.

Q: I've watched you from the beginning on this one. Isn't there an easier way to make a billion dollars? [Laughter]

A: In MiniMed, we were initially selling stock at $1.75 a share. When I sold the company to Medtronic in 2001, we got $192 split twice. So we'll see. I hear someone on the Internet, someone of substance, suggesting MannKind's stock would be $70 a share at some point. I haven't seen it, so cannot comment myself.

That's assuming Al's goal is to make a billion dollars. He has got a few of those already. He's trying to do something for diabetes.

My objective is to solve this problem. Afrezza is probably the most significant contribution to solving this. If you combine this with a basal pump, that would be an enormous contribution to the world, and economically feasible as well.

Q: Given your motivation to help the diabetes community, why don't you price under pens so that more people can use it?

A: No. Keep in mind that we start with insulin, there is processing cost, the cost of the device. The fact that we can do for essentially the same price is quite remarkable. We also require more insulin, since not all of it gets into the lungs. Our objective is a single digit premium but no more. We've met with large groups of insurance companies, and for that range, they will quickly reimburse.

--by Adam Brown, Hannah Deming, Hannah Martin, Manu Venkat, and Kelly Close