CLOSER LOOK

JP Morgan Healthcare Conference

January 11-14, 2016: San Francisco, CA; Day #2 Highlights - Draft

Executive Highlights

Hello from our home base in San Francisco, as the JPM festivities continue! Day #2 showcased some diabetes giants including AZ, Dexcom, Lilly, Roche, and more - see below for our top highlights and if you're interested to see what's coming next in the home stretch, take a look at our preview.

Top Highlights - Diabetes Technology

1. Dexcom CEO Kevin Sayer headlined his talk with the customary 4Q15 revenue pre-announcement: estimated revenue was ~$129 million, a striking ~23% sequential rise from record-high 3Q15 revenue, and a 53% year-over-year gain (!) on a very tough comparison to a blowout 4Q14. Mr. Sayer also shared Dexcom's global patient base: ~140,000-150,000 as of December 31, with an estimated ~20%-25% outside the US. Pipeline commentary below (no major updates).

2. Roche COO Mr. Roland Diggelmann shared muted perspective on the company's Diabetes Care business, but new plans to submit its novel CGM to regulatory authorities in the EU ("definitely" in 2016) and US ("definitely not" in 2016).

3. Confident Insulet CEO Patrick Sullivan largely reiterated recent quarterly calls in his standing-room-only presentation, though Q&A shared a notable commitment to prioritize mobile app development, with potential applications to the artificial pancreas.

Top Highlights - Diabetes Drugs

1. Sanofi shared a slew of timeline updates for its mid- to late-stage diabetes products and expressed confidence in LixiLan's (lixisenatide/insulin glargine) potential.

2. In a breakout session, Lilly shared that it expects a US regulatory decision in 2Q16 or 3Q16 on a label change to reflect the cardioprotective benefit for Jardiance (empagliflozin).

3. AZ management offered an optimistic take on the potential for cardioprotection with Farxiga (dapagliflozin) and expressed confidence in a path forward for its saxagliptin/dapagliflozin fixed-dose combination after speaking with the FDA.

4. Amgen's presentation highlighted the upcoming CV outcomes data for Repatha (evolocumab), now expected in 2H16, and the drug's strong reimbursement position.

5. In a combined Pfizer/Allergan panel discussion, Allergan management expressed enthusiasm for Pfizer's SGLT-2 inhibitor ertugliflozin and PCSK9 inhibitor bococizumab.

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Top Highlights - Diabetes Technology

1. Dexcom CEO Kevin Sayer headlined his talk with the customary 4Q15 revenue pre-announcement: estimated revenue was ~$129 million, a striking ~23% sequential rise from record-high 3Q15 revenue, and a 53% year-over-year gain on a very tough comparison to a blowout 4Q14. Estimated full-year revenue came in at ~$400 million, rising 54% YOY from 2014 and smashing the updated $350-$375 million guidance and original $340-$360 million guidance issued at JPM 2015. Mr. Sayer said the G5 launch has been a "huge hit," and "people love not carrying the receiver" (see diaTribe's test drive). Management also disclosed the estimated global patient base for the first time in over a year: ~140,000-150,000 as of December 31, 2015, with an estimated 75%-80% in the US (~113,000) and ~20%-25% (~33,000) outside the United States. On guidance, Dexcom expects 2016 revenue in the range of $540 million-$565 million (35%-41% growth YOY). Notably, spending this year will include a major ~$40 million investment on several key initiatives: the next-gen CGM partnership with Verily (Google Life Sciences - the largest spend), increased manufacturing capacity (a second factory in Arizona), an "advanced data platform, and international expansion. There were no major pipeline updates, though Dexcom now expects to launch the new insertion system ("one button push, you don't feel it"), smaller G5 transmitter, and new receiver in "late 2016 or early 2017" (slightly behind the 3Q15 guidance to launch these products in 2H16). The company is still in regular discussions with FDA to obtain an insulin-dosing claim, though management "would love get it done before 2016 is over." Remarks positioned it as a competitive barrier to entry for the first time: "We will undoubtedly be the first company to have this label. And we want to set the bar high. You've got to have a sensor that performs as well as ours does." See below for more details on the business and pipeline, including new commentary on the Verily partnership (lots of enthusiasm), automated insulin delivery (Bigfoot called out as "thinking differently"), G6 (sounds delayed due to FDA discussions on the dosing claim), Medicare coverage (potentially in 2017), and FreeStyle Libre.

2. Roche COO Mr. Roland Diggelmann shared muted perspective on the company's Diabetes Care business, but an update on plans to submit its novel CGM to regulatory authorities in the EU ("definitely" in 2016) and US ("definitely not" in 2016). The CE Marking timeline could represent a step back from previous guidance (to "launch" by the end of 2016), though with a near-term submission and speedy approval, year-end commercialization is still possible. New to us, it sounds like an EU pivotal trial is already underway, but Mr. Diggelman did not share any specifics (Is the trial recruiting? When is completion? What is the size, length, comparison, etc.). In the US, Mr. Diggelman alluded to a more stringent regulatory process slowing things down, though it does sound like stateside commercialization is on the radar. Indeed, it's very encouraging to hear that Roche is pushing forward on CGM given how challenging the BGM business has been (see below). As sensors get more accurate, more connected, smaller, much cheaper, and factory calibrated, glucose monitoring might start to shift more meaningfully to sensors in the next decade. In that sense, Roche needs to move quickly on CGM to stay competitive in the crowded glucose monitoring landscape. However, Roche will have to be thoughtful about differentiating its offering from established players, and we certainly think there is an uphill battle ahead given the greater experience and next-gen innovation happening at Abbott (FreeStyle Libre), Dexcom (G5), and Medtronic (Enlite 3). What will set Roche's CGM apart?

- **Commentary on the BGM business touched on: (i) the steep challenges in the US; (ii) the strength of the business in Latin America, Europe, and emerging markets; and (iii) the staunch commitment to this vertical.** As expected, Mr. Diggelmann was quite guarded in discussing the US market - contextualizing Roche's performance with the caveat that "all the largest companies are suffering" - but suggested that the business is trending in the right direction. International performance sounds like it remains strong and is driving positive margins for the business as a whole. This was good to hear though reminded us how significant the margins must

have been before competitive bidding! Mr. Diggelman shared that the US market has lost ~80% of its strip sales since July 2013, though the redeeming quality for industry is that the number of patients in this market continues to grow. [Another question is whether the number of patients self-monitoring their blood glucose continues to grow; with more and more therapies that don't cause hypoglycemia, plus tighter payer restrictions on strips, we wonder how much bigger this market is getting.] Ultimately, it sounds like BGM remains attractive to Roche, who is riding out the storm in the US. It does not sound like significant changes or reorganization are on the horizon, though significant BGM innovation may not be either.

- **Roche did not devote much time to its diabetes pharmaceutical pipeline, though CEO Mr. Alan Hippe did remark bluntly on declines for Lucentis (intravitreal ranibizumab) - "It was not really a fantastic year."** As in previous updates, he attributed weakness to increased competition for Lucentis in diabetic macular edema (DME) and age-related macular degeneration. He was "not that frustrated," however, given the strong way Lucentis initially came out of the gate. Mr. Hippe also shared that expanded indications for Lucentis in ophthalmology will help sales long term. He commented both on Roche's phase 2 port delivery system study for Lucentis in the treatment of ocular disease ("a challenging technology but I think we're moving in the right direction") and a study investigating Lucentis in wet age-related macular degeneration has been moved into phase 2. These solutions are still a ways down the line though it's encouraging to see Roche advancing innovation in eye disease.

3. Confident Insulet CEO Patrick Sullivan largely reiterated recent quarterly calls in his standing-room-only presentation, though Q&A shared a notable commitment to prioritize mobile app development, with potential applications to the artificial pancreas. Management excitedly highlighted the "best-in-class" Glooko data management partnership announced last week (early feedback has been excellent), and Chief Commercial Officer Shacey Petrovic shared future "Digital Insulet" plans in Q&A: (i) launch of a non-regulated Insulet app in 1H16 (importing data from Glooko, reordering pods, training, help); (ii) a 2016 FDA 510(k) submission of the next-gen PDM with Bluetooth and a paired Insulet app that integrates Dexcom G5 CGM data (approval expected in late 2016-early 2017, slightly behind the 3Q15 plan to firmly launch in 2016); and (iii) building Bluetooth directly into the pod for the artificial pancreas, which could even enable dosing from the phone (still under discussion, and a backup device might be required). More color and timelines on the AP program are expected in the 4Q call in February. Management was also excited about yesterday's expanded partnership with Lilly to develop a Humalog U200-compatible OmniPod handheld, building on the existing U500 partnership (clinical trial to complete in December). Ms. Petrovic said the U200 handheld has a two or three-year development cycle. Today's talk did not provide any Q4 revenue pre-announcement or a specific patient base number (roughly 60,000-70,000 US patients, based on what was said today), though one metric caught our eye: >50% of patients who choose OmniPod would NOT have otherwise switched to a pump. Combined with ~70% of Insulet patients still coming from MDI, there should be lots of room for Insulet to grow the market. Mr. Sullivan concluded that he is "even more excited" to be at Insulet than when he joined 15 months ago, and despite quality and inventory issues in 2015, "the company is performing extraordinarily well." As we understand it, Insulet is considering an Investor Day to be held sometime in 2016; we hope to hear more on the February call. More details below on company strategy (reiterating recent calls), expansion in 2016 in Europe, pipeline, marketing, and profitability.

Top Highlights - Diabetes Drugs

1. Sanofi shared a slew of timeline updates for its mid- to late-stage diabetes products and expressed confidence in LixiLan's (lixisenatide/insulin glargine) potential. Most notably, Sanofi plans to launch phase 3 programs in type 2 diabetes in 4Q16 for its newly-licensed SGLT-1/2 dual inhibitor sotagliflozin (from Lexicon) and ultra-long-acting GLP-1 agonist efpeglenatide (from Hanmi). In addition, Sanofi shared that results from the SORELLA phase 3 trial of its insulin lispro biosimilar candidate is expected in 2Q16. The company also highlighted the recent FDA submission of GLP-1 agonist/basal insulin combination LixiLan (EU submission coming in 1Q16). Management confirmed that, due to the use of a

priority review voucher (PRV) for LixiLan, standalone Lyxumia (lixisenatide) and LixiLan should both receive regulatory decisions in 3Q16. During the breakout session, head of Diabetes and Cardiovascular Ms. Pascale Witz noted that Sanofi is "very satisfied" with the phase 3 LixiLan results. During a conversation with us, Zealand management suggested that Sanofi's decision to spend its expensive (reportedly $245 million) PRV on LixiLan implies that the phase 3 results were impressive (Zealand licensed Lyxumia and LixiLan to Sanofi and has not yet seen the full results). For its part, Novo Nordisk suggested in its 3Q15 update that it expects its GLP-1 agonist/basal insulin combination Xultophy (insulin degludec/liraglutide) to have a significantly stronger clinical profile than LixiLan. Zealand management also felt that the effect of short-acting lixisenatide on post-prandial glucose excursions may be an important point of differentiation in the market. We assume that could also lead Sanofi to position LixiLan primarily as a means to intensify basal insulin, though Sanofi was fairly cagey on that topic in the breakout session. In any case, we agree with Zealand's assessment that the use of the PRV reflects Sanofi's strong commitment to LixiLan. Indeed, Sanofi reiterated that one of its key strategic goals within diabetes is to develop its insulin glargine franchise, including Lantus (insulin glargine), Toujeo (U300 insulin glargine), and LixiLan. Sanofi management also shared that the company will be stepping up its overall R&D expenses to comprise 15%-15.5% of its total sales.

2. In a breakout session, Lilly shared that it expects a US regulatory decision in 2Q16 or 3Q16 on a label change to reflect the cardioprotective benefit for Jardiance (empagliflozin). The 2Q16 timeline is based on a six-month priority review process. EMPA-REG OUTCOME data for Jardiance has also been submitted in the EU and EU submission for Synjardy is expected this quarter. In addition, Lilly expressed strong confidence that the EMPA-REG OUTCOME data will catalyze a change to Jardiance's indication, rather than just resulting in a change to the efficacy data in the label. As mentioned in its recent 2016 financial guidance call, Lilly believes that the updated label will be the first of two significant inflection points in Jardiance sales; the second will be updated treatment guidelines that position Jardiance more favorably. The company hopes that Jardiance will be positioned as an option along the entire continuum of care for type 2 diabetes, from the start of therapy to patients already on insulin at high cardiovascular risk. Despite the company's high hopes, however, the recently-updated 2016 AACE/ACE guidelines offered a conservative take on the EMPA-REG OUTCOME results. The new algorithm made no changes to prescribing recommendations even for the specific high-risk population group tested. The algorithm does mention a "possible benefit" of SGLT-2 inhibitors on atherosclerotic cardiovascular disease (ASCVD) but designates the class as neutral for heart failure. In other updates, Lilly shared that it plans to initiate a phase 3 program for Adocia-partnered BioChaperone Lispro in 2016, shared that it is gaining market share in every diabetes drug category in the US, Europe, and Japan, and offered commentary on the current outcry over drug pricing - see our detailed report below for more.

3. AZ management offered an optimistic take on the potential for cardioprotection with Farxiga (dapagliflozin) and described the SGLT-2 inhibitor class as potentially transformative. When asked during the breakout session whether AZ expected its US diabetes business to grow in the next couple of years, CEO Mr. Pascal Soriot expressed great confidence in Farxiga's growth potential following the positive EMPA-REG OUTCOME results for Lilly/BI's Jardiance (empagliflozin). He suggested that the SGLT-2 inhibitor class has yet to fully take off due to inertia among primary care providers but that it will eventually "transform the way diabetes is treated." We could certainly imagine the class becoming the standard second-line treatment for type 2 diabetes, at least for high-risk patients, if the results are replicated in other studies. AZ management appeared fairly confident that the results will be replicated in DECLARE (Farxiga's CVOT), noting that the phase 3 meta-analysis of CV outcomes for Farxiga was very similar to that for Jardiance. Management even suggested that the trial could potentially be stopped early if interim analyses in 2016 and 2017 show a significant benefit; trial completion is currently expected in 2019. We do expect that the benefit is most likely a class effect given the minimal differences between the three agents, though we would shy away from putting too much stock in the meta-analyses due to the small number of events included. AZ also highlighted DECLARE's inclusion of a lower-risk "primary prevention" population in addition to the higher-risk patient population comparable to that in EMPA-REG OUTCOME; this should make the DECLARE results particularly informative for treatment guidelines.

- **AZ remains confident in a path forward for its saxagliptin/dapagliflozin ("saxa/dapa") fixed-dose combination after speaking with the FDA.** AZ had reassured investors in its 3Q15 update that the Complete Response Letter for saxa/dapa was not due to concerns about heart failure or DKA but stated that it had yet to meet with the FDA about the path forward. The company has now met with the FDA and remains confident in the product's future; management promised more details in its 4Q15 update on February 4. On the contrary, management stated that AZ has still not received an update from the FDA on label additions for DPP-4 inhibitor Onglyza (saxagliptin) due to the SAVOR results. We would certainly expect any updates to arrive soon given that the Advisory Committee meeting on the topic took place almost nine months ago.

4. Amgen's presentation highlighted the upcoming CV outcomes data for Repatha (evolocumab), now expected in 2H16, and the drug's strong reimbursement position. In his review of key recent and upcoming launches, CEO Mr. Bob Bradway characterized Repatha as a very important growth opportunity for Amgen in the next few years. He noted that the ongoing FOURIER CVOT for the product is expected to complete by mid-2016, so results will be available within the year. This is an earlier timeline than we might have expected, as investigator Dr. Marc Sabatine (Brigham and Women's Hospital, Boston, MA) indicated at last year's ACC that results were expected "no later than 2017," and the estimated completion date on ClinicalTrials.gov is February 2018. Amgen management appeared quite optimistic about the results during Q&A. Our outlook is fairly positive as well given the impressive LDL reductions seen with Repatha in phase 3 and the clear link between LDL lowering and CV outcomes in past trials. Mr. Bradway also noted that data from an intravascular ultrasound (IVUS) study of Repatha is also expected in 2H16 and suggested that it could be quite compelling to cardiologists by providing visual evidence of regression of atherosclerosis. On the payer front, Mr. Bradway shared that Repatha will have access to 81% of the US commercial market in 2016 - no doubt helped by a favorable position on both the Express Scripts and CVS Health formularies. This strong start suggests that US payers remain willing to cover expensive new therapies that are significantly differentiated even in a more cost-conscious environment (albeit with restrictions on patient eligibility - this will be especially important to unpack in diabetes). It will be interesting to see whether this is also true for more historically cost-conscious European payers as reimbursement discussions proceed there.

- **Not to be outdone, Sanofi shared that UnitedHealthcare has decided to offer preferred access to its PCKS9 inhibitor Praluent (alirocumab).** UnitedHealthcare, the third-largest pharmacy benefits manager (PBM) in the US after Express Scripts and CVS Health, will not include competitor Repatha on its formulary. Previously, Express Scripts had announced that it would include both Praluent and Repatha on its formulary while CVS Health chose to award an exclusive formulary contract to Repatha. Nonetheless, Sanofi was proud of the 150 million covered lives with access to Praluent now - we're not sure how this number compares with the "81% of the commercial market" that has access to Repatha. In the breakout session, Sanofi management suggested that the concurrent approval timelines for Praluent and Repatha have contributed to the many exclusive formulary access deals for PCSK9 inhibitors. In addition, Sanofi shared that its CVOT for Praluent is fully enrolled and interim data will be available in the second half of 2016 (full results by the second half of 2017).

5. In a combined Pfizer/Allergan panel discussion, Allergan management expressed enthusiasm for Pfizer's SGLT-2 inhibitor ertugliflozin and PCSK9 inhibitor bococizumab. The two companies' management discussed topics surrounding their recent merger, with relatively high-level commentary on synergy targets, R&D approaches, and more. Most notably, when asked about specific areas of excitement in each other's pipelines, Allergan management briefly pointed to Pfizer's Merck-partnered SGLT-2 inhibitor ertugliflozin - as a reminder, we learned yesterday from Merck that filings for the candidate are anticipated in 2016. Management also commented that Pfizer's PCSK9 inhibitor bococizumab will be promising, as there is "really intriguing work" going on that may "point PCSK9 inhibitors in a different direction compared to competitors." We heard similar commentary from Pfizer during its 3Q15 update of the potential behind bococizumab's different mechanism of action. While it will certainly be interesting to see

how the phase 3 clinical data compare, we would expect payer coverage for this class to be the biggest differentiator. For more on this pipeline and its latest, please see our coverage of Pfizer's 3Q15 update.

Detailed Discussion and Commentary

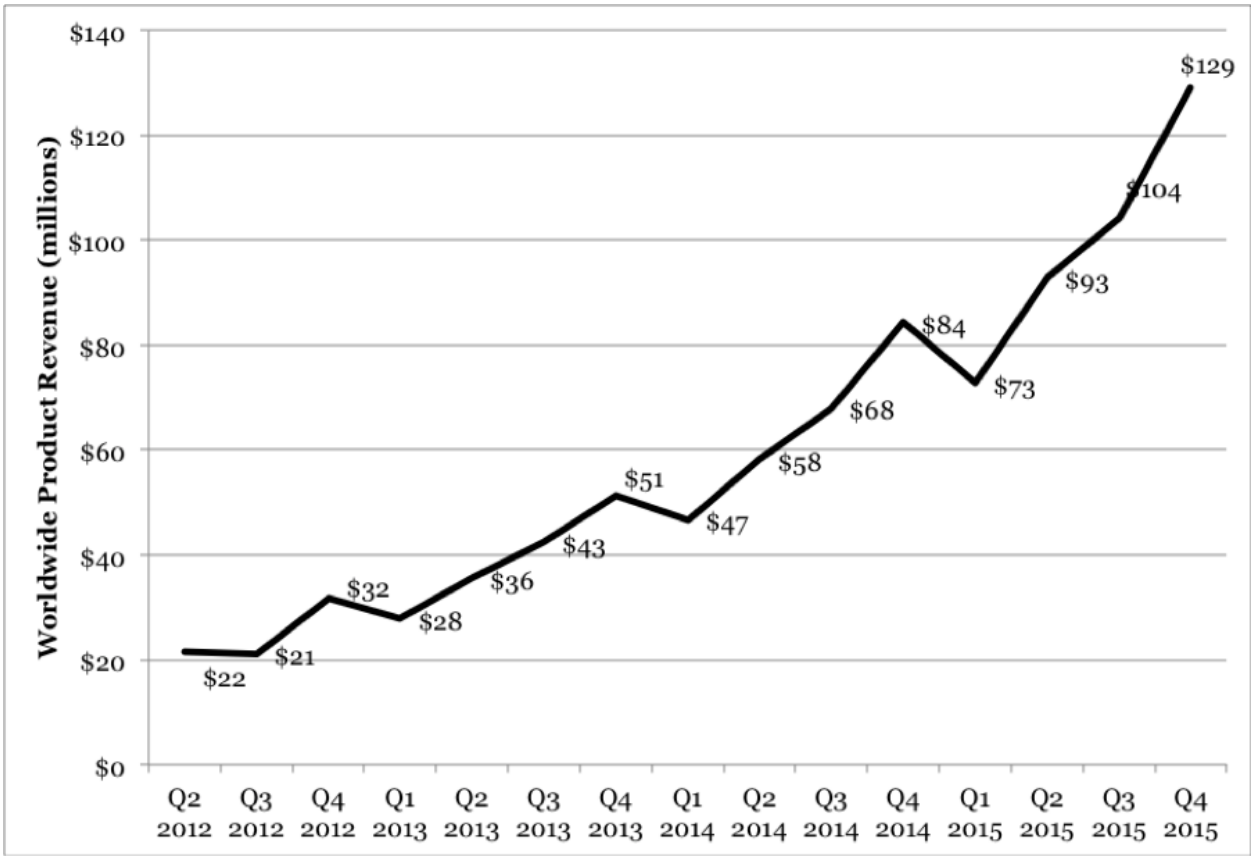
JP Morgan Public Company Presentations

DEXCOM

Kevin Sayer (CEO, Dexcom, San Diego, CA)

Dexcom CEO Kevin Sayer headlined his talk with the customary 4Q15 revenue pre-announcement: estimated revenue was ~$129 million, a striking ~23% sequential rise from record-high 3Q15 revenue, and a 53% year-over-year gain on a very tough comparison to a blowout 4Q14. Estimated full-year revenue came in at ~$400 million, rising 54% YOY from 2014 and smashing the updated $350-$375 million guidance and original $340-$360 million guidance issued at JPM 2015. Mr. Sayer said the G5 launch has been a "huge hit," and "people love not carrying the receiver" (see diaTribe's test drive). Management also disclosed the estimated global patient base for the first time in over a year: ~140,000-150,000 as of December 31, 2015, with an estimated 75%-80% in the US (~113,000) and ~20%-25% (~33,000) outside the United States. On guidance, Dexcom expects 2016 revenue in the range of $540 million-$565 million (35%-41% growth YOY). Notably, spending this year will include a major ~$40 million investment on several key initiatives: the next-gen CGM partnership with Verily (Google Life Sciences - the largest spend), increased manufacturing capacity (a second factory in Arizona), an "advanced data platform, and international expansion. There were no major pipeline updates, though Dexcom now expects to launch the new insertion system ("one button push, you don't feel it"), smaller G5 transmitter, and new receiver in "late 2016 or early 2017" (slightly behind the 3Q15 guidance to launch these products in 2H16). Dexcom is still in regular discussions with FDA to obtain an insulin-dosing claim, though management "would love get it done before 2016 is over." Remarks positioned it as a competitive barrier to entry for the first time: "We will undoubtedly be the first company to have this label. And we want to set the bar high. You've got to have a sensor that performs as well as ours does." See below for more details on the business and pipeline, including new commentary on the Verily partnership, automated insulin delivery, G6, Medicare coverage, and FreeStyle Libre. This company continues to fire on all cylinders - topline revenue, bottom line profitability, pipeline, and commercial execution. Can it sustain the momentum in 2016 and beyond?

- **Dexcom reported estimated 4Q15 revenue of ~$129 million, a strong ~23% sequential rise from record-high 3Q15 revenue, and a 53% year-over-year gain on a very tough comparison to a blowout 4Q14.** Estimated full-year revenue was ~$400 million, rising 54% YOY from 2014 and smashing the updated $350-$375 million guidance (which was increased from the original $340-$360 million guidance issued at JPM 2015). This now marks 13 straight quarters of 49%+ YOY growth for Dexcom since the launch of G4 in late 2012. Talk about serious business and pipeline execution. Mr. Sayer put the growth into perspective quite well: in 2011, Dexcom's full-year revenue was 40 million, meaning sales have increased 10-fold in five years.



- **Dexcom's estimated global patient base was ~140,000-150,000 as of December 31, 2015, with an estimated 75%-80% in the US (~113,000) and 20%-25% (~33,000) residing outside the United States**. This represents an ~60% rise from ~90,000 patients as of the JPM 2015 update (when management reported ~50% patient base growth in 2014). Assuming 1.5 million type 1s in the US, that puts Dexcom's CGM penetration in type 1 at ~8%, and total CGM penetration in type 1 in the ~10-15% range. Management said international patients buy fewer sensors and purchase less frequently than US patients - the lack of CGM reimbursement is still forcing many EU patients to pay out of pocket.
- **Management expects 2016 revenue in the range of $540 million-$565 million (35%-41% growth YOY),** with a seasonal 15% sequential decline expected from 4Q15 to 1Q16. Obviously as Dexcom's base of sales grows, it cannot maintain 50%+ YOY growth; analysts in the room seemed to agree that the growth expectation for next year was very reasonable.
- **Dexcom expects increases in cash-based net income in 2016 (improved profitability), though management plans to invest ~$40 million on several key infrastructure and pipeline initiatives:**
    - **the partnership with Verily** [Google Life Sciences] "to really change the face of CGM" and penetrate into type 2 (the biggest expense);
    - **increased manufacturing capacity** (a second US factory in Arizona with more automation);
    - **an "advanced data platform"** (with millions of G5 data points flowing in every day, Dexcom needs to analyze it and do something valuable with it);
    - **international expansion** (reimbursement is "getting close" in several countries, and Dexcom plans to establish a European headquarters; the company has generated all of its International revenue with just four people.

- **Dexcom now expects to launch the new insertion system ("one button push, you don't feel it"), smaller G5 transmitter, and new receiver in "late 2016 or early 2017."** This timing is slightly behind the 3Q15 guidance to launch these products in 2H16. These are major operational and pipeline undertakings for Dexcom - the hardware improvements are lower cost and will offer a better patient experience, but also require a major manufacturing overhaul.
- **Mr. Sayer was enthusiastic about the Verily [Google Life Sciences] partnership, noting strong synergies as the two companies seek to develop a flexible, disposable, bandage-like, 10-14-day CGM the size of a penny. In his view, the biggest obstacle is not technology, but cost.** Mr. Sayer said both companies are teaching each other - for example, the original CGM patch Google showed did not have enough processing power for CGM data, nor did it have a Bluetooth radio. On the other hand, the Verily team is teaching Dexcom to think outside of their traditional type 1 perspective - e.g., non-insulin-using type 2s don't need a sensor as robust as the G4/G5. That perspective could enable tradeoffs on product form factor that could make it smaller and less expensive. Mr. Sayer is confident that the pieces will come together from a technology perspective. The bigger concern is cost - Dexcom has cost targets to meet on the insertion and sensor, and Google has targets on the electronics. We would love to know what the target price is! Is it $10 per sensor? $20 per sensor?
    - **Regarding timing of the Verily partnership, management said that it "will take five years to get there"** (i.e., flexible, low-cost, bandage-like, disposable CGM sensor/ transmitter the size of a penny to be worn on the body for 10-14 days). When the initial partnership was announced last August, the first product was expected to be commercialized in two to three years, with a follow-on product to be commercialized within five years. We assume Mr. Sayer's five-year comment referred to the follow-on product, but are not positive.
    - **Based on today's commentary, it does sound like the Verily sensor will have Bluetooth connectivity, but will probably be less robust and full-featured than Dexcom's current type 1-focused G4/G5.** Management said the portfolio may see a divergence once the Verily product launches: the core type 1 product with a premium price and more features (e.g., G5, G6, and beyond), and the simpler, low-cost type 2 product with Verily. This was consistent with remarks upon the partnership's announcement last August, though at the time, we were unsure about accuracy or connectivity. We assume the Verily product will be factory calibrated - given the type 2 audience - but are not sure.
- **Dexcom is still in regular discussions with FDA to obtain an insulin-dosing claim. Management "would love get it done before 2016 is over." Remarks positioned it as a competitive barrier to entry for the first time:** "We will undoubtedly be the first company to have this label. And we want to set the bar high. You've got to have a sensor that performs as well as ours does." This is a smart move against Abbott's FreeStyle Libre, which is slightly less accurate than G4/G5 (MARD ~11% vs. 9.0%), but of course adds factory calibration and 14-day wear. An inability to obtain a dosing claim would definitely hurt FreeStyle Libre's compelling "no fingersticks" marketing in the US. Dexcom-FDA discussions still center on what data needs to be collected pre- and post-market to enable the label claim. But in new news, management said discussions also include "patient training," and as the two parties keep jumping over hurdles, others keep coming up. Management said the dosing claim is "not a simple filing" (e.g., like a new sensor) - "This is more of a process. We're writing the book on our industry and what it's going to look like. We're being very thoughtful." In the 2Q15 call, a dosing claim was expected in 2016, while the 3Q15 call did not provide a timeline.
    - **Connected to the dosing claim, management said Medicare coverage "might" come in 2017 ("a couple years away").** This has been long-awaited and it will be an amazing advocacy and regulatory victory to get this in motion once a dosing claim is approved. CEO Kevin Sayer did not sound highly optimistic about the bills in Congress.

- **G6 has been delayed in anticipation of the insulin dosing claim. In the meantime, Dexcom might proceed with the trials, targeting one calibration per day and 10-day wear.** In the 2Q15 call, management expected to begin a G6 pre-pivotal study in late 2015, with a pivotal study to shortly follow, an FDA submission in early 2016, and launch in early 2017. It does not sound like any G6 trials have commenced, and we'll look for more color and timing on the 4Q15 call in February.
- **Management was pressed in Q&A on FreeStyle Libre, expressing confidence it is not having an impact on Dexcom's uptake in Europe. Interestingly, management noted that Dexcom's G5 label in Europe has a stronger dosing claim than FreeStyle Libre (see below).** We're not sure this is really driving patients to choose one system over another - Abbott can still heavily market "no fingersticks" - but it was an interesting point. Otherwise, management reminded analysts that FreeStyle Libre is not a CGM, though Abbott "has done some things really well" (e.g., cost, factory calibration, on-body form factor, disposable). After another pressing question on FreeStyle Libre's cost advantage, management acknowledged that if FreeStyle Libre is "good enough" for patients out there, Dexcom "can follow." We look forward to the competition - many patients are going to benefit from better products from both companies!
    - **Dexcom EU Label:** *"The G5 Mobile System is designed to replace fingerstick blood glucose testing for diabetes treatment decisions."*
    - **Abbott EU Label***:* "The FreeStyle Libre Flash Glucose Monitoring System is indicated for measuring interstitial fluid glucose levels in adults aged 18 years and older. It is designed to replace blood glucose testing in the self-management of diabetes with the exceptions listed below" (rapidly changing glucose levels, hypoglycemia, if symptoms do not match).
- **Management said its insulin pump partners are "moving as aggressively as they can" on G5, G6, and artificial pancreas integration. Management called out Bigfoot Biomedical for thinking differently about automated insulin delivery.** Today's remarks reiterated Dexcom's commitment to enabling automated insulin delivery, and Mr. Pacelli said it has challenged its partners to "not just follow Medtronic, but to come out with something competitively better than Medtronic" (1Q15 was the first time we heard this). Some of these novel approaches, said Mr. Pacelli, are more "software driven," while others are more "hardware driven." Mr. Pacelli called out Bigfoot Biomedical, who is "starting fresh" and approaching the problem differently - "Everybody is carrying a super computer in their pocket: a phone. Why replicate that into another product?" To what extent Bigfoot will leverage smartphones is unclear, but it confirms comments Jeffrey Brewer made at ADA 2015. We'll see a Bigfoot demo tomorrow for the first time, which should give more color on the approach. "The problem" startup companies like Bigfoot have, said Mr. Pacelli, is "lack of a commercial infrastructure." We wonder if Dexcom would help co-promote artificial pancreas products, or perhaps aid in other ways.
    - **EVP Steve Pacelli refrained from commenting on the plans to accelerate the MiniMed 670G** (see our Day #1 report), though he did point out that Medtronic has not presented any data on the next-gen sensor. We have heard anecdotally that Enlite 3 is better than the original Enlite (see our ATTD 2015 coverage: MARD: 11% vs. YSI; MARD: 13% vs. fingersticks at camp).
- **Dexcom is also considering CGM-enabled decision support for patients on MDI.** The company is evaluating intelligent pens that transmit insulin data to the phone, and combined with CGM data, algorithms could give dosing advice (Mr. Pacelli dubbed this, "a poor man's artificial pancreas"). Such an approach would be much lower cost than an artificial pancreas, but provide patients with valuable behavior and decision support tools.
- **"DME is a tough business. We need this to go to the drug store." Reiterating comments from the past few calls, management expressed a strong desire to move CGM reimbursement to pharmacy distribution.** "With a $129 million quarter, I get emails from someone who is unhappy about the time spent on the phone. Almost every time, I can take it back to

a complicated insurance issue where Dexcom was negotiating on behalf of the patient. We need patients to go to the drug store instead." As of the 3Q15 call, the goal was to move 70% of the business to pharmacy benefits as the primarily reimbursement source over a three-year period.

- **In 2H16, Dexcom still expects early data from the DiaMond study (n=338, 24 months, testing CGM in MDI users) and European reimbursement studies.** These trials are critical to show the therapeutic and cost benefits of full-time CGM use regardless of insulin delivery method. Dexcom has always fought an uphill battle with some HCPs, as many prescribe pumps first or suggest CGM to those only on pumps.
- **CEO Kevin Sayer pointed out AACE/ACE's strong endorsement of CGM in type 1 and type 2 following the 2014 Consensus Conference on Glucose Monitoring:** "CGM is recommended in all patients with type 1 diabetes and should be available to all type 2 diabetes on multiple insulin injections, basal insulin, or sulfonylureas. CGM should also be used in all patients who are at risk for hypoglycemia and/or have hypoglycemia unawareness" (Grunberger et al., *Endocrine Practice* 2015). Our coverage is here.

INSULET

Patrick Sullivan (CEO, Insulet, Billerica, MA)

Confident Insulet CEO Patrick Sullivan largely reiterated recent quarterly calls in his standing-room-only presentation, though Q&A shared a notable commitment to prioritize mobile app development, with potential applications to the artificial pancreas. Management excitedly highlighted the "best-in-class" Glooko data management partnership announced last week (early feedback has been excellent), and Chief Commercial Officer Shacey Petrovic shared future "Digital Insulet" plans in Q&A: (i) launch of a non-regulated Insulet app in 1H16 (importing data from Glooko, reordering pods, training, help); (ii) a 2016 FDA 510(k) submission of the next-gen PDM with Bluetooth and a paired Insulet app that integrates Dexcom G5 CGM data (approval expected in late 2016-early 2017, slightly behind the 3Q15 plan to firmly launch in 2016); and (iii) building Bluetooth directly into the pod for the artificial pancreas, which could even enable dosing from the phone (still under discussion, and a backup device might be required). More color and timelines on the AP program are expected in the 4Q call in February, though we're glad to hear the sustained commitment - a mobile system would differentiate Insulet from Medtronic's MiniMed 670G (poised to be first to market), and keep it competitive with a potential mobile offering from Bigfoot. Management was also excited about yesterday's expanded partnership with Lilly to develop a Humalog U200-compatible OmniPod handheld, building on the existing U500 partnership (clinical trial to complete in December). Ms. Petrovic said the U200 handheld has a two or three-year development cycle. Today's talk did not provide any Q4 revenue pre-announcement or a specific patient base number (roughly 60,000-70,000 US patients, based on what was said today), though one metric caught our eye: >50% of patients who choose OmniPod would NOT have otherwise switched to a pump. Combined with ~70% of Insulet patients still coming from MDI, there should be lots of room for Insulet to grow the market. Mr. Sullivan concluded that he is "even more excited" to be at Insulet than when he joined 15 months ago, and despite quality and inventory issues in 2015, "the company is performing extraordinarily well." As we understand it, Insulet is considering an Investor Day to be held sometime in 2016; we hope to hear more on the February call. More details below on company strategy, expansion in 2016 in Europe, pipeline, marketing, and profitability.

- **Insulet estimates it has ~4% market share of ~1.7 million type 1s in the US, meaning its US installed base is roughly 70,000 patients.** [Note: Insulet only provided the 4% and 1.7 million numbers today; a patient base number is expected on the Q4 call.] Management estimates one-third of US type 1s are using a pump - despite multiple pump companies growing their businesses over the past few years, this number has not seemed to change much. These metrics translate to a ~12% US pump market share for Insulet, which sounds about right based on revenue.
- **Insulet currently has 70 US territories (a 40% expansion in 2015) and 150 field sales reps.** Each territory includes a territory manager and one clinical sales manager (CDE by training).

- **OmniPod launches in 2016 with partner Ypsomed are expected in Denmark, France, Finland, Belgium, and Luxembourg.** The OmniPod is currently sold in the US, Canada, and 10 EU countries. "Future markets" include Poland, Spain, China, Saudi Arabia, UAE, Qatar, and Australia - there was no timing attached, but we assume the European launches are much nearer term and launches like China are more mid-term.
- **Over time, Insulet will prioritize functionality in its future mobile app, with less functionality in the handheld itself**. This move makes sense, as the phone offers more customization, a better user experience, stronger use of the data, easier product updates, and more. The one downside to this strategy is it may isolate some patients less interested in phone integration. Even for the Dexcom G5, we know of many patients who continue to use the receiver instead of the phone app. Still, fewer features in the PDM could also improve the cost profile of the handheld, a key differentiator.
- **An "important slide" highlighted Insulet's four key R&D areas to leverage the OmniPod "platform technology."** It was notable to see the new Glooko partnership (only announced last week) in one of the four spots - a clear testament to management's confidence in the partnership.
    - **Concentrated insulins for type 1 diabetes and type 2 diabetes.** This now spans Lilly's U500 insulin and U200 Humalog. Management estimates these products will double Insulet's current addressable market. As a reminder, the OmniPod can hold 200 units, not enough capacity for those requiring high doses of insulin (the leader is Tandem's 480-unit t:flex).
    - **Glooko**: Announced last week, the partnership significantly improves OmniPod data management for physicians and patients, integrating OmniPod, BGM, CGM, and activity data. In addition to Glooko's patient-facing mobile app and web dashboard, Glooko provides clinics with a downloading kiosk tablet. Insulet is making Glooko free nationwide for OmniPod patients and prescribing clinicians. Patients on Android can download their OmniPod directly onto the Glooko mobile app; those using iPhone can use the web dashboard. Once Insulet's next-gen Bluetooth PDM is out, we assume the data will go directly into the Glooko app.
    - **CGM integration and artificial pancreas**: Insulet continues to develop its next-gen Bluetooth-enabled OmniPod, with submission expected this year and approval by end of 2016 or early 2017 (slightly behind the 3Q15 plan to firmly launch it by end of 2016). The PDM will launch with an Insulet app to display OmniPod pump and Dexcom CGM data. Further down the line, Insulet may build Bluetooth into the pod itself, offering potential for closed-loop dosing from a smartphone. That would be compelling artificial pancreas product, assuming the FDA is willing to approve an algorithm solely running on a standard smartphone. Management said a "backup device" may be needed, which sounds pretty likely to us - even Dexcom's G5 required a receiver to be sold, even if patients don't use it.
    - **Drug delivery**: Management's excitement remains sky high on this business vertical, which got as much airtime as the OmniPod business in prepared remarks. Consistent with prior quarterly calls, Insulet has several agreements in place, but it will take ~3-5 years to fully launch any of them (Amgen took five years from concept to launch).
- **JP Morgan Analyst Mike Weinstein pressed management on the path to profitability in Q&A, though commentary largely sidestepped the question.** The new management team was willing to take some hits to profitability last year, as investment were needed to improve product quality. We see these as worthwhile for patient safety and confidence, though Mr. Weinstein had broader concerns - is the current manufacturing process and the Ypsomed distribution partnership (which has sub-30% margins) hindering profitability? Management also didn't address the profitability of the Neighborhood Diabetes business, which certainly reduces gross margins.

Profitability is obviously a goal, though we're glad to see the team making major investments in R&D - these will be key to stay competitive in the highly dynamic pump market.

- **Mr. Sullivan still hopes Insulet can be a $1 billion+ company, though he suggested it will take five to six years (~2020-2021).** In his remarks at JPM 2015, he hoped this could happen by 2019. Perhaps the upside on drug delivery will take longer than expected to be realized.
- **Mr. Sullivan's prepared remarks echoed recent commentary on the company's strategy:** expanding marketing efforts to focus on physicians and payers (vs. just patients alone); compiling and communicating clinical data; continued optimism for the future drug delivery business (years away from significant revenue, but a whole section of the presentation); and full installation of an experienced senior management team (many of whom have worked together previously). More specifics can be found in our 2Q15 and 3Q15 coverage.

SANOFI

Olivier Brandicourt (CEO, Sanofi, Paris, France)

Sanofi shared a slew of timeline updates for its mid- to late-stage diabetes products and expressed confidence in LixiLan's (lixisenatide/insulin glargine) potential. Most notably, Sanofi plans to launch phase 3 programs in type 2 diabetes in 4Q16 for its newly-licensed SGLT-1/2 dual inhibitor sotagliflozin (from Lexicon) and ultra-long-acting GLP-1 agonist efpeglenatide (from Hanmi). In addition, Sanofi shared that results from the SORELLA phase 3 trial of its insulin lispro biosimilar candidate is expected in 2Q16. The company also highlighted the recent FDA submission of GLP-1 agonist/basal insulin combination LixiLan (EU submission coming in 1Q16). Management confirmed that, due to the use of a priority review voucher (PRV) for LixiLan, standalone Lyxumia (lixisenatide) and LixiLan should both receive regulatory decisions in 3Q16. During the breakout session, head of Diabetes and Cardiovascular Ms. Pascale Witz noted that Sanofi is "very satisfied" with the phase 3 LixiLan results. During a conversation with us, Zealand management suggested that Sanofi's decision to spend its expensive (reportedly $245 million) PRV on LixiLan implies that the phase 3 results were impressive (Zealand licensed Lyxumia and LixiLan to Sanofi and has not yet seen the full results). For its part, Novo Nordisk suggested in its 3Q15 update that it expects its GLP-1 agonist/basal insulin combination Xultophy (insulin degludec/liraglutide) to have a significantly stronger clinical profile than LixiLan. Zealand management also felt that the effect of short-acting lixisenatide on post-prandial glucose excursions may be an important point of differentiation in the market. We assume that could also lead Sanofi to position LixiLan primarily as a means to intensify basal insulin, though Sanofi was fairly cagey on that topic in the breakout session. In any case, we agree with Zealand's assessment that the use of the PRV reflects Sanofi's strong commitment to LixiLan. Indeed, Sanofi reiterated that one of its key strategic goals within diabetes is to develop its insulin glargine franchise, including Lantus (insulin glargine), Toujeo (U300 insulin glargine), and LixiLan. Sanofi management also shared that the company will be stepping up its overall R&D expenses to comprise 15%-15.5% of its total sales.

- **Sanofi shared that UnitedHealthcare has decided to offer preferred access to its PCKS9 inhibitor Praluent (alirocumab).** UnitedHealthcare, the third-largest pharmacy benefits manager (PBM) in the US after Express Scripts and CVS Health, will not include competitor Repatha on its formulary. Previously, Express Scripts had announced that it would include both Praluent and Repatha on its formulary while CVS Health chose to award an exclusive formulary contract to Repatha. Nonetheless, Sanofi was proud of the 150 million covered lives with access to Praluent now - we're not sure how this number compares with the "81% of the commercial market" that has access to Repatha. In the breakout session, Sanofi management suggested that the concurrent approval timelines for Praluent and Repatha have contributed to the many exclusive formulary access deals for PCSK9 inhibitors. In addition, Sanofi shared that its CVOT for Praluent is fully enrolled and interim data will be available in the second half of 2016 (full results by the second half of 2017).
- **Sanofi reiterated its strong belief that dual agonists represent the next wave of innovation for both type 1 and type 2 diabetes.** Management noted that Sanofi has both a

GLP-1/glucagon dual agonist and a GLP-1/GIP dual agonist in phase 1. Both were highlighted in more detail in the company's November "Meet Sanofi Management" seminar.

- **Sanofi was clear that its diabetes strategy moving forward is portfolio expansion.** In particular, management noted that while the biosimilar insulin lispro is an aspect of its portfolio, the company is pursing a transformation with its mid- to late-stage pipeline that will allow the portfolio to evolve to include drug classes other than insulin.
- **Lexicon already has a phase 3 study for sotagliflozin in type 1 diabetes underway** and Lexicon management emphasized in the company's 3Q15 update that there are no plans to slow down the type 1 diabetes program. That said, the FDA has previously signaled a preference for an integrated type 1 and type 2 development program over a solo type 1 development program and may delay approval in type 1 diabetes until the data package for type 2 diabetes is complete.

LILLY

John Lechleiter (CEO, Lilly, Indianapolis, IN)

In a breakout session, Lilly shared that it expects a US regulatory decision in 2Q16 or 3Q16 on a label change to reflect the cardioprotective benefit for Jardiance (empagliflozin). The 2Q16 timeline is based on a six-month priority review process. EMPA-REG OUTCOME data for Jardiance has also been submitted in the EU and EU submission for Synjardy is expected this quarter. In addition, Lilly expressed strong confidence that the EMPA-REG OUTCOME data will catalyze a change to Jardiance's indication, rather than just resulting in a change to the efficacy data in the label. As mentioned in its recent 2016 financial guidance call, Lilly believes that the updated label will be the first of two significant inflection points in Jardiance sales; the second will be updated treatment guidelines that position Jardiance more favorably. The company hopes that Jardiance will be positioned as an option along the entire continuum of care for type 2 diabetes, from the start of therapy to patients already on insulin at high cardiovascular risk. Despite the company's high hopes, however, the recently-updated 2016 AACE/ACE guidelines offered a conservative take on the EMPA-REG OUTCOME results. The new algorithm made no changes to prescribing recommendations even for the specific high-risk population group tested. The algorithm does mention a "possible benefit" of SGLT-2 inhibitors on atherosclerotic cardiovascular disease (ASCVD) but designates the class as neutral for heart failure. In other updates, Lilly shared that it plans to initiate a phase 3 program for Adocia-partnered BioChaperone Lispro in 2016, shared that it is gaining market share in every diabetes drug category in the US, Europe, and Japan, and offered commentary on the current outcry over drug pricing - see our detailed report below for more.

- **Lilly shared that it plans to initiate a phase 3 program for Adocia-partnered ultra-rapid-acting insulin BioChaperone Lispro in 2016.** Lilly management previously characterized the clinical development program for the candidate as "progressing extremely well" in its 3Q15 update. This presentation also reiterated a series of key events for 2016, first shared in the company's 2016 Financial Guidance update. Diabetes-related events included phase 3 data from the MARLINA study of Tradjenta (linagliptin) in patients with renal impairment, US regulatory submission of empagliflozin/metformin XR, and regulatory actions on the label additions for Jardiance CV outcomes data, EU submission of Glyxambi, and US submission of linagliptin/ metformin XR.
- **Lilly proudly highlighted its "most complete portfolio of diabetes products in the industry" and shared that the company is gaining market share in every diabetes drug category in the US, Europe, and Japan.** Lilly spotlighted its particularly prolific series of diabetes drug launches in the last 18 months, including Jardiance (empagliflozin), Trulicity (dulaglutide), Glyxambi (empagliflozin/linagliptin), Humalog U200 KwikPen, Synjardy (empagliflozin/metformin), and Basaglar (biosimilar insulin glargine). We've been particularly impressed by Trulicity's ramp up in sales this year (reaching $74 million in 3Q15), and its patient-friendly ease-of-use has contributed to growth in the GLP-1 agonist class as a whole. Lilly management also noted today and previously during its financial guidance update that the new-to-

brand (NBRx) share for Jardiance is now 25%, up from 15% before the release of the EMPA-REG OUTCOME topline results.

- **Lilly management also offered thoughts on the public and political outcry over drug pricing, suggesting that the pharmaceutical free market is essentially sound and will not likely change.** Echoing sentiments from the company's 3Q15 update (and Gilead's breakout session from JPM Day #1), management indicated that the pharmaceutical industry needs to do a better job with its messaging and put the focus back on new breakthroughs and cures while reminding the public that the driver of healthcare costs is chronic diseases rather than prescription drug costs. This is certainly true on a systemic level, though prescription drug costs can pose significant burdens for individuals. In addition, management pointed a finger at payers, asking why "commercial insurance puts such a disproportionate burden of consumer spending on drugs." Lilly emphasized that it is "on the side of the patient" and pointed to its prescription assistance programs as evidence of its commitment to improving access to its products. On the other hand, Dr. Irl Hirsch has previously railed against prescription assistance programs as creating pent-up demand for products that weaken payers' position in formulary access negotiations.
    - **While acknowledging that the political rhetoric around drug pricing will be particularly intense in an election year, management stressed the importance of not overreacting and underscored the importance of keeping the "right policies" in place at the legislative level**. Ultimately, Lilly doesn't believe that the fundamental free market principles underlying the drug industry will change, but noted that the industry should not take that for granted either. To that end, Lilly concluded with the importance of "making sure these things are understood by thought-leaders." We assume this means the pharmaceutical industry lobby will be particularly strong in Washington this coming election cycle. For more on the complex issue of drug pricing, see our thoughts from our 2015 + 2016 Reflections piece.

ASTRAZENECA BREAKOUT SESSION

Q: Do you have any updates on the response to the saxa/dapa CRL?

A: In 3Q15 we communicated that we hadn't talked to the FDA but we were confident there would be a path forward. We have now talked to the FDA and we are still confident. We'll give more specific information in our 4Q15 update.

Q: Have you heard anything about potential label updates for Onglyza based on the SAVOR results?

A: We have no update. This is in the hands of regulators. They have all the information they need to understand the benefit/risk profile of the product and they haven't communicated anything to us. We anticipate that they will digest the information and have an interaction with us, but they haven't communicated anything.

Q: Do you expect your diabetes business in the US to grow for the next one or two years?

A: One product that can definitely grow is Farxiga. That should really transform the treatment of diabetes. The problem is there's a lot of apathy in the system. Endocrinologists have changed their practice but with primary care providers it takes time. We have a class that reduces CV risk and theoretically should be adopted quickly, but it takes time for primary care providers to adopt because they're creatures of habit. They still use a lot of SUs. It will take time, but that class will transform the way diabetes is treated.

Q: But you haven't demonstrated a benefit yet.

A: The key question is really more when [than if]. We have done a meta-analysis of phase 3 and saw the same benefits as Lilly saw with empagliflozin. The question is how quickly we can get the data. We do have a safety study with CV outcomes, DECLARE. It enrolls 17,000 patients. 7,000 of them look like EMPA-REG OUTCOME and 10,000 are a new patient population, primary prevention. We'll have interim analyses in 2016 and 2017 and expect final results in 2019. That timing will be driven by the primary prevention population

where events accrue more slowly. We'll see how the DSMB reacts to the interim data and if they need to come to us and say something's happening and we can't maintain a placebo group. If that happens at the first interim, it will be driven by the secondary prevention group. You can't have that with primary prevention in that amount of time. It's a hard outcome to predict when the timing will be. The upside opportunity for us is to have data on primary prevention.

Q: I thought a third member of the class didn't replicate that. There was an initial bolus of events with canagliflozin, but didn't it level out to just a slight advantage over time?

A: It doesn't look like the patient population was quite the same as in EMPA-REG OUTCOME, so that's one thing it's confounded by. We have EMPA-REG and then we're guided by our meta-analysis. That's not fileable, but it's enough to say what we think is happening and that it looks pretty similar to EMPA-REG.

AMGEN BREAKOUT SESSION

Q: You have two important clinical readouts for Repatha coming up. Can you put the significance of the IVUS study into perspective given its close proximity to the CVOT?

A: We see the IVUS data as complementary to the outcomes data. Obviously if we had to choose, we would choose the outcomes data, but the IVUS data is extremely compelling to cardiologists. A picture's worth a thousand words. When you can actually see regression of the underlying atherosclerosis, that's extremely impactful to physicians. That can potentially be represented in the label and eventually promoted. It does appear in the statin labels. It's a potential differentiating factor for us as we're the only company doing this kind of trial. The data will demonstrate the underlying mechanism by which the outcomes benefit is generated.

Q: How does it fit into your discussions with payers?

A: People are aware of the outcomes study and this trial. I believe the utilization management criteria will be changed once we have both sets of data.

Q: Express Scripts talked about their program for Repatha and how they aim to guarantee access to the right patients. Can you provide more color on the nature of that agreement?

A: We don't disclose details, but clearly the way our team developed Repatha gave a clear, definitive view of what the drug does: intensive, predictable LDL lowering. Identifying a high-risk cardiovascular patient with atherosclerosis is pretty simple. We're working to identify what the prior authorization process is, how to identify patients, but you're looking at almost a guarantee of LDL lowering.

Q: Can you comment on the potential for neurotoxicity with PCSK9 inhibitors?

A: The recent source of all that was an anonymous online post - there may be a less valuable source of information on the planet but I'm not familiar with it. It's complete hocus pocus. That said, this is a novel mechanism being investigated in humans for the first time. We don't believe the drugs have meaningful penetration through the blood-brain barrier, so these are mostly theoretical concerns. The issue is that cholesterol is an important constituent of cell membranes, and you can hypothesize endless adverse events if the physiology is starved of cholesterol. That ignores the fact that cholesterol is manufactured in the body at will and these therapies don't impact that. Plus the antibodies don't get into the CNS.

One thing you have to remember when you see extremely small imbalances in people complaining about irritability and memory is that you can't achieve 100% blinding. Anyone can get their cholesterol checked, and patients do this in the trials, so they know they're on a drug that dropped their cholesterol by 75%. Then they have a bias toward reporting that they woke up and felt fuzzy. It's never the bottle of wine they drank the night before. Look at the labeling; that's what we understand. There are very large placebo-controlled studies going on across the industry with close to 100,000 patients, so we'll learn the safety profile. You might also ask what safety problems might arise that would offset the benefit of reducing these cardiovascular outcomes by the magnitude we're expecting in the outcomes studies.

-- by Melissa An, Adam Brown, Helen Gao, Varun Iyengar, Emily Regier, Ava Runge, and Kelly Close