Closer Look

MEMORANDUM

J&J 2Q14 - Global Diabetes Care down 5%, US down 14%; strong performance for Invokana, new phase 2 trial in type 1 diabetes - July 15, 2014

Executive Highlights

- Global Diabetes Care sales totaled $558 million in 2Q14, falling 5%. The US blood glucose monitoring business declined 14% year-over-year and rose 16% sequentially. International sales increased 2%.
- Invokana continued its strong performance, with ~$90 million in sales in 2Q14, a rise in prescriber share from 1Q14, and approvals in 45 countries to date, with more on the way in 2014. We still expect the compound to reach close to $500 million in sales in 2014.
- Notably, J&J has registered a phase 2 trial investigating Invokana in type 1 diabetes patients on ClinicalTrials.gov, with a May 2015 estimated primary completion date.

Early this morning, Johnson and Johnson CEO Mr. Alex Gorsky led the company's 2Q14 financial update. We're bringing you our top five highlights from the call, including the financial and pipeline updates for both Diabetes Care (LifeScan BGM and Animas insulin pumps) and SGLT-2 inhibitor Invokana (canagliflozin). With the one-year anniversary of the implementation of competitive bidding on July 1, J&J Diabetes Care experienced its smallest declines both worldwide and in the US since 4Q13. Although we heard many device pipeline updates during J&J's Medical Devices and Diagnostics Day in May, management did not share any updates this morning in BGM or insulin delivery. In fact, it was disappointing to hear during Q&A that J&J is not "projecting an approval timeline" for the Animas Vibe integrated with the Dexcom G4 Platinum CGM (an ongoing 15-month FDA review at this point) - that said, we remember other device companies having to repeatedly change timelines so we can't say we blame them.

Invokana sales in 2Q14 held relatively steady sequentially at somewhere around ~$90 million, based on our estimates. The sequential comparison was fairly challenging here, as Invokana grew from between ~$40-$75 million in 4Q13 to ~$89 million in 1Q14, which was driven in part by an inventory benefit so although the sequential change looks flat, it is not. The more striking results, in our view, were management's mentions that Invokana now holds a 2.3% total script share (TRx) in the US type 2 diabetes market (excluding insulin and metformin), up from 1.8% in 1Q14 (a 25%-plus increase) while the type 2 diabetes new-to-brand (NBRx) share among US endocrinologists (excluding insulin and metformin) is leading the field at around 17%. In Europe, Invokana received a positive ruling from UK's NICE (which makes large-scale reimbursement decisions) but a negative ruling from Germany's IQWiG (read our report). Management also highlighted the European approval of Vokanamet (Invokana/metformin IR fixed dose combination) in April; Vokanamet has been re-submitted to the FDA (following its previous CRL) and J&J expects a decision in August 2014. An extended release (XR) version of Vokanamet remains in phase 3 in the US.

Excitingly, though not mentioned on the call or J&J's pipeline because we guess it's on the stealth side, we found a fresh phase 2 trial on ClinicalTrials.gov investigating Invokana in type 1 diabetes (ClinicalTrials.gov Identifier: NCT02139943) - this news follows on the heels of AZ's announcement of a phase 3 trial for Forxiga (dapagliflozin) in type 1 diabetes to begin later this year and a new phase 2 trial of Lexicon's SGLT-1/2 inhibitor LX4211 in younger adults with type 1 diabetes, and we are glad to see J&J getting into the game. Even more notable, as previously reported, Invokana is being investigated as a treatment for diabetic nephropathy in the CREDENCE trial. Read on below for more details, as well as a selection of diabetes-related Q&A.

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TOP FIVE HIGHLIGHTS

1. Though Diabetes Care (LifeScan BGM and Animas insulin pumps) still comprises the largest share of J&J's diabetes business, we anticipate that Invokana's relative contribution will continue to grow over time. The US BGM market remains extremely challenging, primarily due to price decreases stemming from competitive bidding that took effect over one year ago (J&J's US Diabetes Care business has now declined for eight consecutive quarters). By contrast, management cited Invokana multiple times as a driver of strong pharmaceutical sales in 2Q14 - notably, management remarked that it contributed more than 2.5 percentage points to overall US pharmaceutical growth in 2Q14, which was a staggering 37% in the quarter (mainly due to the recently launched hepatitis C drug Olysio). As discussed below, we estimate Invokana sales were between $84 million and $93 million (comparable with estimated 1Q14 sales of ~$80-97 million). With growth in the second half of the year, the drug could approach $500 million in sales for 2014 - that would already put it at ~25% of the size of the ~$2 billion Diabetes Care business after just seven quarters on the market (by the end of the year).

- **J&J CEO Alex Gorsky said during the call that type 2 diabetes is becoming "much more manageable" for patients due to the increasing availability of oral antidiabetic agents.** We would agree that oral agents like SGLT-2 inhibitors represent valuable treatment options for patients, as they are easy to take, require little titration, do not cause hypoglycemia, and do not promote weight gain. That said, there are still vast management challenges in type 2 diabetes, with only ~50% of patients at their A1c goal and a mere 14% of patients hitting all four goals for A1c, blood pressure, LDL cholesterol, and nonsmoking (Ali et al., *NEJM* 2013)

2. Worldwide Diabetes Care revenue from LifeScan BGM and Animas pumps totaled $558 million in 2Q14, down 5% as reported and operationally year-over-year (YOY). This was a particularly easy comparison, with worldwide Diabetes Care falling 13% in 2Q13. We'd note that this is the ninth consecutive quarter in which worldwide Diabetes Care sales have declined; on a bit of an encouraging note, however, this is, at least, the smallest decline seen since 4Q12, as J&J is coming off five straight quarters of double-digit negative growth. Sequentially, worldwide Diabetes Care sales grew 9%, compared to a 9% decline from 4Q13 to 1Q14.

- **US Diabetes Care revenue reached $222 million, dropping 14% YOY**. This was a striking improvement from both 2Q13 (when sales declined 23% in the US) and 1Q14 (when sales declined 32%), though of course these challenging quarters contributed to easy comparisons for 2Q14. Sequentially, US revenue increased 16% on a very easy comparison to 1Q14, representing the first time US revenue has grown sequentially in eight quarters (since 1Q12). The US declines may be tapering as competitive bidding has annualized at this point. Still, the US base of sales in 1Q14 was an extremely low starting point for 2Q14 revenue - 2Q14 revenue of $222 million is the third lowest ever US revenue in our model, following only 1Q14 ($192 million) and 4Q13 ($219 million).
    - **Encouragingly, the 1Q14 slide deck noted that the US sales decline was partially offset by volume growth** - we assume attributable to the OneTouch VerioSync, which launched in January and also to more people in the US having at least some coverage. During Q&A, management commented that both the insulin pump business and Animas are seeing "improving performance," and the company expects that that it will soon be "lapping" competitive bidding (i.e., year-over-year comparisons will be on more similar footing, as competitive bidding was implemented one year ago in 2Q13

(July 1, 2013). Indeed, we would have expected to see a little bit more of a "reset" this quarter in the US as competitive bidding annualized, but the dramatic 68% reduction in test strip pricing leaves a long road to rebound.

- **International Diabetes Care sales reached $336 million, rising 2% (as reported and operationally) and 5% sequentially**. This was an easier comparison relative to 2Q13, when sales fell 2% as reported and 1% operationally. As we understand it, Russia and Ukraine have been very fast growing markets for J&J, and we wonder whether instability in the regions will impact the company's international growth in the foreseeable future.
    - **At J&J's Medical Devices and Diagnostics Day, we learned that J&J recently signed an agreement with Nova Biomedical Corporation in China. The agreement will deliver point-of-care glucose testing using OneTouch products.** This was not mentioned on today's call, but it should expand the company's reach in an international market with lots of potential for growth.
- **During Q&A, management once again commented that J&J "remains committed to its diabetes space" -** this point has been re-emphasized in recent calls, given the challenges in the US and the company's reorganization of its Diabetes Care business. J&J has been hardest hit by current market forces in BGM, a direct result of the company's strength in the US relative to other players. Despite the encouraging sequential growth this quarter, we expect there are still obstacles ahead, particularly if US payers seek to renegotiate contacts towards CMS-like reimbursement. In our view, the near-term future of diabetes care will still include BGM, but the margins and level of innovation are both sure to decline in the new normal.
- **We will be interested to see how the financials for the rest of the Big Four blood glucose monitoring companies (Abbott, Bayer, and Roche) look as we come up on the one-year anniversary of competitive bidding implementation** - and if the rest of these companies are still feeling the heat of the implementation. For background, Abbott US Diabetes Care fell 28% in 1Q14 and 7% in 2Q13, Roche North America Diabetes Care grew 6% as reported in 1Q14 and fell 8% in 2Q13, and Bayer US Diabetes Care fell 40% in 1Q14 (not reported in 2Q13). Abbott reports its 2Q14 results tomorrow (Wednesday) morning, Roche reports July 24, and Bayer reports July 30.
- **On a depressing note for patients, management commented that it was not "projecting an approval time" on the Animas Vibe integrated with the Dexcom G4 Platinum CGM (an ongoing 15-month FDA review at this point).** This was an update for us, as J&J's Medical Devices and Diagnostics Day in May said that the company had responded to the FDA's questions "recently this year" and the device would be in the US by the end of 2014. This is a disappointment, as the FDA review has now more than doubled the statutory six-month PMA review cycle. Ms. Ashley McEvoy (Chair of Diabetes Care and Vision Care) called the product a competitive "sore spot" at the Medical Devices and Diagnostics Day. Remarks on the device pipeline were otherwise sparse.
    - **There were no updates on Calibra's three-day, wearable, bolus-only Finesse insulin delivery device -** management highlighted during the Medical Devices and Diagnostics Day that it would be launched within 24 months (now in the next ~22 months).
    - **We additionally heard no updates on the two unspecified BGM filings** listed during the Medical Devices and Diagnostics Day (one in 2014 and one in 2015), although we suspect that one could refer to a Next Generation OneTouch UltraVue Verio in Japan and the other a Next Generation Glucose Testing Platform.

3. We estimate that US sales of the SGLT-2 inhibitor Invokana (canagliflozin) were $84-$93 million in 2Q14. Management said that Invokana contributed more than 2.5 percentage points to overall US pharmaceutical growth in 2Q14 (which was a staggering 36.6%, driven largely by J&J's new hepatitis C drug Olysio); by our calculations (and assuming that values up to 2.75 would be rounded to 2.5), this gives a

range of $84-$93 million for 2Q14. This range is comparable to the $80-$97 million in sales we estimated in 1Q14, which represented a dramatic rise from the $45-75 million we estimated in 4Q13. This quarter was Invokana's fifth full quarter on the market, and the third quarter that J&J gave an indication of its financial performance. Invokana received its own slide during management's prepared remarks, where its launch was again characterized as the most successful US launch for an oral type 2 diabetes agent since Merck's DPP-4 inhibitor Januvia (sitagliptin).

- **Invokana has achieved 2.3% of total prescription (TRx) share in the US diabetes market (excluding insulin and metformin), up from 1.8% in 1Q14.** TRx among US endocrinologists (also excluding insulin and metformin) grew from roughly 6% in 1Q14 to 7% in 2Q14. New-to-brand (NBRx) prescription share among US endocrinologists appears to be holding steady at around 17%, making Invokana the US market leader in this regard (as of the end of June, according to IMS data).
- **Invokana had several major international launches in 1H14, including in the UK, Germany, Mexico, Canada, and Singapore; it is now approved in 45 countries.** This is the first time J&J has mentioned launches in specific European countries since the drug was approved in Europe in November 2013.
    - **Management did not break out international sales for Invokana, but we did learn recently about two divergent reimbursement decisions on Invokana in Europe.** The UK's National Institute for Health and Care Excellence (NICE) announced its final appraisal of Invokana late last month, granting it a positive recommendation (read our report) that preserves optimal reimbursement for the drug (for most patients). However, the German Federal Joint Committee's (G-BA's) Institute for Quality and Efficiency in Health Care (IQWiG) recently handed down a "no additional benefit" comparative effectiveness assessment for Invokana, which (if confirmed by the final G-BA ruling) would relegate the product to the realm of generic-level pricing (see the second half of our report). Based on these results, we would expect stagnant or declining sales in Germany, with building momentum in the UK. However, we hope that the public and patient voice in Germany might prompt the G-BA to diverge from IQWiG's negative assessment. The G-BA usually follows IQWiG's recommendations, but it is not required to. According to the presentation slides, Invokana has also received positive reimbursement rulings in Switzerland and the Netherlands.
- **Invokana will likely face increased competition in the SGLT-2 inhibitor market in the near future, although the compound's first-in-class status in the US will remain an advantage.** Other benefits of Invokana include its looser restrictions for use in the renally impaired population compared to AZ's Farxiga and its lack of ever having been associated with bladder cancer (as the FDA once was concerned with with Farxiga). AstraZeneca's Farxiga (dapagliflozin) was approved in the US in January 2014 (and was already approved in Europe under the trade name Forxiga in November 2012, ahead of Invokana). Lilly/BI resubmitted their SGLT-2 inhibitor Jardiance (empagliflozin) to the FDA in June 2014; our understanding is that the re-review process will take approximately two months since reportedly the only issue with the original submission was a defect at BI's manufacturing plant that has since been resolved. Jardiance was recently approved in Europe in May 2014. Other earlier stage SGLT-2 inhibitors in development include Pfizer/Merck's ertugliflozin (phase 3), Astellas/Kotobuki's ipragliflozin (approved in Japan), Taisho's Lusefi (luseogliflozin; approved in Japan), Islet Sciences/BHV Pharma's remogliflozin etabonate (phase 2), Theracos' THR1442 (phase 2), Lexicon's SGLT-1/SGLT-2 dual inhibitor LX4211 (phase 2 for type 1 and type 2 diabetes), and Novartis' SGLT-1/SGLT-2 dual inhibitor LIK066 (phase 2).

4. Notably, a new trial investigating Invokana in type 1 diabetes is listed as recruiting on ClinicalTrials.gov (Identifier: NCT02139943). This randomized, double-blind, placebo-controlled study has an estimated enrollment of 330 patients and a forecasted primary completion date of May 2015. Though this was not discussed in the call, we believe it is a significant development that is part of a larger

trend of exploration of type 2 diabetes drug classes (especially SGLT-2 inhibitors) in type 1 diabetes. SGLT-2 inhibitors have been considered particularly useful candidates for type 1 diabetes because of their insulin-independent mechanism of action - Dr. Anne Peters (USC, Los Angeles, CA) discussed the (currently off-label) application of Invokana in type 1 diabetes at this year's Clinical Diabetes Technology Meeting as well as at the recent Children with Diabetes Friends for Life 2014 meeting. AZ also recently announced plans to initiate a phase 3 trial of Forxiga/Farxiga in type 1 diabetes patients by the end of the year. Lexicon and the JDRF recently announced a collaboration on a new phase 2 trial of the SGLT-1/2 dual inhibitor LX4211 in a relatively young and poorly controlled adult type 1 diabetes patient population (read our report).

- **J&J's pharmaceutical pipeline continues to list Invokana as phase 3 for a diabetic nephropathy indication.** This was one of the more exciting news items in our view from J&J in 1Q14, and we had suspected that J&J might pursue a nephropathy indication for Invokana after the initiation of the CREDENCE renal outcomes trial. An indication for diabetic nephropathy would confer great differentiation to Invokana over other SGLT-2 inhibitors, though with CREDENCE's primary completion date of February 2019, the indication may not come for quite some time. To our knowledge, there are no other SGLT-2 inhibitors under investigation for a nephropathy indication, but the theorized mechanism would suggest that any renal-protective benefits of Invokana could be a class effect. Diabetic nephropathy remains an area of great unmet need, as no current treatments are capable of reversing kidney damage; however, Reata's former drug bardoxolone is being tested anew, as we found our recently - we await further word on this.
- **We saw some new long-term safety and efficacy data on Invokana at this year's ADA.** Dr. Bruce Bode (Atlanta Diabetes Associates, Atlanta, GA) presented the results of a 78-week extension of a 26-week primary study on the effects of J&J's Invokana (canagliflozin) in elderly (age 55 -80) type 2 diabetes patients (n=521 completers). Invokana 300 mg (the higher dose) led to a placebo-adjusted A1c reduction of -0.60% from a relatively low baseline of 7.7%. This represented a very slight (and not surprising) rise in A1c from the week 26 results (-0.70%). Canagliflozin also caused sustained reductions in fasting plasma glucose, body weight, and blood pressure. The incidence of serious adverse events, which are of particular concern in older patients, were similar for treatment and control groups. Another study presented in the same session explored the temporal changes in urinary glucose excretion, urine volume, and plasma volume seen with Invokana treatment, suggesting that most (but not all) adverse effects in these regard disappear after 12 weeks of treatment.

5. As previously announced, management pointed out that Vokanamet (Invokana/metformin immediate release) was approved in Europe in April 2014; it is currently under review with the US FDA with a PDUFA date in August 2014. The approval of this fixed-dose combination (FDC) follows the positive CHMP opinion that J&J received in February and the European approval of AZ's Xigduo (Forxiga/metformin IR fixed-dose combination) in January 2014. Vokanamet was resubmitted to the FDA in February 2014 after receiving a complete response letter in December 2013. The FDA requested data demonstrating that the twice-daily dosing regimen of Vokanamet was comparable to that of the once-daily dosing of the approved Invokana single agent.

- **J&J's Invokana/metformin extended release (XR) FDC remains in phase 3 in the US.** This agent, if approved, would allow for once-daily dosing, which is not possible with SGLT-2 FDCs using immediate release metformin. This XR FDC is not being pursued in Europe given that metformin XR is not available there.
- **We are excited about the prospects for such combination therapies**; very few patients are controlled on metformin alone, and ultimately the vast majority will need at least two or three drugs as their disease progresses. While SGLT-2 inhibitor/metformin FDCs are intriguing, the real combination potential for SGLT-2 inhibitors arguably lies in their combination with DPP-4 inhibitors. We saw phase 3 data demonstrating strong efficacy of 1.0%-1.5% with AZ's saxa/dapa and Lilly/BI's empa/lina at ADA (read our ADA 2014 SGLT Inhibitors Report). We have not heard much from J&J management on the prospect of a combination with another DPP-4 inhibitor, but given

Invokana's status as a first-in-class agent, we believe such an effort is ripe for the taking with that or another oral class.

QUESTIONS AND ANSWERS

Q: Diabetes in the US remains challenged, but it was a little less challenged than I expected this quarter. Are we close to our turning point? When do you think that we'll get back to where we were before? When will we see a full OUS launch for Vibe and where are you in the filing?

A: We remain committed to the diabetes space. There was a significant - I think 75% price reduction - in the US during the first half of last year. So we do expect to be lapping that soon. If we look at the underlying dynamics of the market, I would like to commend our team because we continue to see a very good performance. That's SMBG both in the US as well as outside. With our insulin pump business, and Animas, we're seeing improving performance. Another important dynamic is that our Diabetes Care business also has been involved in the launch of Invokana. Part of the early success with Invokana has been that we're able to offer a broader more comprehensive offering to the endocrinologists who we have very strong relationships with. That's better for patients, physicians, and our business.

Q: When will we see the full outside-US launch, and where are you with the US filings and launch?

A: We do have the Vibe under review by FDA. I don't believe we're projecting an approval time at this point, but we certainly think that it's going to offer a nice addition for patients as well as for physicians.

Q: How big of an accelerator do you think it will it be to have the combination of metformin and Invokana in a single administration?

A: We're very pleased with the launch of Invokana. It's been the most successful launch in type 2 diabetes since Januvia, and we are now the leading oral anti-diabetic in type 2 diabetes among US endocrinologists. The most relevant combination we have of metformin and Invokana is approved in Europe. We're expecting a response from the FDA with a PDUFA date in August. So we think it's going to be an important element for physicians, and we have a significant impact in our business moving forward.

APPENDIX: DEVICE PIPELINE

Pipeline Product	Timeline
Finesse insulin delivery device (acquired from Calibra Medical)	Expected to launch within the next ~22 months; Medical Devices and Diagnostics Day timeline
Animas Vibe Insulin Pump with integrated Dexcom G4 Platinum CGM	Health Canada approval received September 2013. FDA PMA filing submitted in April 2013, and J&J recently responded to FDA questions. Not "projecting approval timing" as of 2Q14.
OneTouch Ping Verio Insulin Pump with Remote Meter	Planned US submission in 2013; no recent updates - potential 2014 filing?
Next Generation OneTouch UltraVue Verio	Planned Japan submission in 2013; no recent updates - potential 2014 filling?
Next Generation Glucose Testing Platform	Planned US and EU submission in 2013; no recent updates - potential 2015 filing?
Predictive Low Glucose Suspend	Inpatient feasibility study of algorithm presented at ADA 2014

Hypoglycemia-Hyperglycemia Mitigation System	Study presented at ADA 2013; no recent updates
Metabolics (surgical care product)	Planned submission in 2013; no recent updates

APPENDIX: DRUG PIPELINE

Drug Name	Class	Indication	Status/ Timeline	Other Remarks
Vokanamet (canagliflozin/ metformin IR)	SGLT-2 inhibitor/ metformin FDC	Type 2 diabetes	Approved in EU; Submitted in US	FDA CRL in December 2013; Resubmitted to FDA in February 2014; PDUFA date August 2014
Vokanamet XR (canagliflozin/metformin XR)	SGLT-2 inhibitor/ metformin FDC	Type 2 diabetes	Phase 3 in the US	Metformin XR is not available in the EU, so this agent would not be marketed there.
Invokana	SGLT-2 inhibitor	Diabetic nephropathy	Phase 3	CREDENCE renal outcomes study has primary completion date in February 2019.
Invokana	SGLT-2 inhibitor	Type 1 diabetes	Phase 2	New phase 2 trial, with primary completion date in May 2015
Invokana	SGLT-2 inhibitor	Type 2 diabetes - pediatric	Phase 1	Trial currently recruiting, primary completion date in December 2014
JNJ-16269110	MTP inhibitor		Last known to be in phase 2	No ongoing trials listed on ClinicalTrials.gov

JNJ-41443532	Insulin sensitizer		Last known to be in phase 2	No ongoing trials listed on ClinicalTrials.gov

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