Closer Look

MEMORANDUM

Merck R&D and Business Briefing - November 10, 2011

Executive Highlights

- MK-3102, Merck's once-weekly DPP-4 candidate, has advanced into phase 2b.
- Merck's Januvia/atorvastatin fixed-dose combination MK-0413E has advanced into phase 3.

Merck conducted its annual R&D and business briefing today in a call led by Dr. Peter Kim, President of Merck Research Laboratories. During the call, the great Dr. Nancy Thornberry, Senior Vice President and Research Head, Diabetes and Endocrinology (we have met her personally and find her an incredibly inspiring leader), provided several interesting diabetes R&D updates. Most notably, Merck has advanced MK-3102, its once-weekly DPP-4 inhibitor candidate into phase 2b. During the call, management noted that MK-3102 is expected to have an efficacy, safety, and tolerability profile similar to that of sitagliptin. Notably, we also learned during Q&A that MK-3102 is not metabolized and therefore is long-lived in the bloodstream. Overall, we'll be watching carefully to see how development of this once-weekly DPP-4 evolves and are eager to learn more details about the science behind its long half-life. In the long term, we assume it will help Merck's strong position in the incretin market. Although once-daily DPP-4s are not as efficacious at lowering A1c as GLP-1s, their uptake has been much better than that of GLP-1s due to more benign side effect profiles, which has made them easier to prescribe for harried GPs - anything that will "move the dial" even a little is something this group (to generalize) seems to find very appealing. All else equal, we assume that the ease of dosing provided by MK-3102 will only strengthen DPP-4's better uptake - although on the downside, it is back to two co-pays for patients, most of whom, we presume, would continue to take other orals daily.

On the fixed-dose combination front, MK-0431E, the company's sitagliptin/atorvastatin fixed-dose combination (FDC), has moved into phase 3 trials. Management guided that it plans to file for the compound in 2014. As a reminder, this will be the fourth Januvia FDC and second Januvia/statin FDC Merck has developed (behind Juvisync, Merck's Januvia/simvastatin combination which the FDA approved in October). Notably, however, Merck is no longer pursuing development of its Januvia/pioglitazone FDC MK-0431C, which was previously in phase 3 trials - this was due to commercial and regulatory concerns.

Dr. Thornberry also highlighted positive-trending cardiovascular safety data for Januvia during the call. Notably, a pooled analysis of 19 double-blind controlled studies of up to two years including more than 10,000 patients and 64 major cardiovascular adverse events (MACE) has shown that the risk for MACE is lower (exposure-adjusted risk ratio 0.68 [95% CI: 0.41, 1.12]), albeit not significantly, with sitagliptin versus comparator treatment. We'll now of course be intensely following what the phase 3 TECOS Trial (n=14,000, ClinicalTrials.gov Identifier: NCT00790205) says about Januvia's cardiovascular safety. As a reminder, this trial is evaluating the cardiovascular outcomes of long-term treatment with sitagliptin used as part of usual care as compared to usual care without sitagliptin. It is expected to complete in December 2014.

Finally, we were excited to hear more about the company's long-term diabetes strategy and its plans regarding SmartInsulin. Dr. Thornberry noted during the call that Merck's diabetes strategy includes maintaining leadership in the DPP-4 inhibitor space via development of the once-weekly DPP-4 inhibitor MK-3102, development of the Januvia/atorvastatin FDC MK-0431E, completion of TECOs, and seeking approval of Janumet XR in the US. Additionally, management commented during Q&A that Merck is making good preclinical progress with SmartInsulin and that the company's long-term goal is to have both short and long-acting SmartInsulins. Yes! (That's all the patients calling ....)

- **MK-3102, the company's novel once-weekly DPP-4 inhibitor, has moved into phase 2b and is anticipated to enter phase 3 in 2012**. During the call, management highlighted data demonstrating that seven days after dosing, MK-3102 10 mg once-weekly provided DPP-4 inhibition on par with that required for maximal clinical efficacy of sitagliptin (80%) - we hope it will be 100% of that of Januvia, since the efficacy of DPP-4 inhibitors isn't their best selling point - it's the ease of use, of course. Management additionally said it anticipated the once-weekly MK-3102 dose will be 25 mg or less and that the compound is expected to have an efficacy, safety, and tolerability profile similar to that of sitagliptin. We also learned during Q&A that MK-3102 is not metabolized and therefore is long-lived in the bloodstream, but specific details on its half-life were not given. Notably, management mentioned during the call that Merck will be focused on making this compound "best-in-class", as compared to "first-in-class" as Januvia was; during the call, management highlighted development of "best-in-class" products in addition to first-in-class products as part of its strategy to improve long-term return on investment. This makes a lot of sense to us and we're very glad to hear Merck's focus is here - it is not surprising, because typically what would limit a company from working hard on "best in class" is funds. We assume there is more cash being invested in diabetes R&D than had previously been planned; by anyone's estimates, Merck's Januvia franchise has outperformed. As a reminder, in September, Takeda announced that it had advanced its once-weekly oral DPP-4 inhibitor SYR-472 into phase 3 trials in Japan. This advancement puts Merck somewhat behind Takeda in the once-weekly DPP-4 inhibitor race, so we'll be interested to see which of MK-3102's characteristics make it "best-in-class" and whether these characteristics can make up for its likely entering the market behind SYR-472. Overall, we'll be watching carefully to see how development of this once-weekly DPP4s evolves and are eager to learn more details about the science behind its long half-life. In the long term, we assume it will help solidify Merck's strong position in the DPP-4 inhibitor market - and in the incretin market more broadly. Although once-daily DPP-4s are generally not as efficacious at lowering A1c (or causing weight loss) as GLP-1s, their uptake has generally been better than that of GLP-1s because of their more benign side effect profiles, which has made them easier to prescribe for harried GPs - anything that will "move the dial" even a little is something this group (to generalize) seems to find very appealing. All else equal, we assume that the ease of dosing provided by MK-3102 will only strengthen DPP-4's better uptake - although on the downside, it is back to two co-pays for patients, most of whom, we presume, would continue to take other orals daily. We also assume that the advent of once-weekly DPP-4s could moderate uptake of Bydureon and the other once-weekly GLP-1s in development (such as Eli Lilly's dulaglutide (phase 3) and Novo Nordisk's semaglutide and liraglutide once-weekly (both phase 2, only one will advance)) as these become available - or, patients would simply begin therapy even sooner. The once-weekly DPP-4 inhibitors seem like they would generate interest to those thinking about R&D and pre-diabetes. Since the once-weekly GLP-1s will still have to be injected and will have (albeit next-gen) GLP-1 characteristic side effects, we imagine that, if the once-weekly oral DPP-4's side effects are as mild as those of the once-daily ones, more patients would be inclined to choose them over once-weekly GLP-1s. In the long term, we'll be interested to see how once-weekly DPP4s affect overall DPP-4 treatment adherence since, as we understand it, adherence is still a problem with this class despite its oral administration and relatively mild side effect profile.
- **MK-0431E, the company's sitagliptin/atorvastatin fixed-dose combination (FDC), has moved into phase 3 trials.** Management guided that it plans to file for the compound in 2014. As a reminder, this will be the fourth Januvia FDC Merck has developed. Merck's Januvia/metformin immediate-release (IR) combination Janumet was approved in 2007 (and its worldwide sales were $350 million in 3Q11, up 41.7% from 3Q10), its Januvia/metformin extended-release combination was submitted to the FDA in 4Q10 and a response is expected in the first quarter of 2012, and its once-daily Januvia/simvastatin FDC Juvisync was approved by the FDA in October. Development of 50 mg doses of the latter compound for people with moderate renal impairment was confirmed during today's call. As we understand it, simvastatin has better HDL-raising abilities than atorvastatin, but atorvastatin is better at lowering LDL, so we assume PCPs' choices of Januvia/statin combination will be driven by their preferences regarding particular patients' HDL and LDL

movements. Notably, however, Merck is no longer pursuing development of its Januvia/pioglitazone FDC MK-0431C, which was previously in phase 3 trials. Management noted that the company had withdrawn its NDA for this compound in Europe due to regulatory and commercial issues associated with the combination. As with Juvisync, we see development of MK-0431E as a big positive for curbing cardiovascular risk in those with type 2 diabetes. Studies have suggested that middle aged-people with type 2 diabetes have comparable risk of having a heart attack as those who have already experienced a heart attack and according to Fu et al. (Curr. Med. Res. Opinion, 2011), only 40% of people with type 2 diabetes who are eligible for statin treatment receive it. We assume Merck's DPP-4/statin combinations, by lowering cost and inconvenience barriers to initiation of statin treatment, will help more people who need statins receive them. More broadly, in our opinion, Merck's pursuit of a wide spectrum of Januvia combination products has been quite smart. Januvia's 2006 launch was easily one of the strongest in diabetes history and the franchise has kept up steady momentum since its introduction (the franchise grew an impressive 41.2% year-over-year in 3Q11). In our view, Merck has been very smart to capitalize on this momentum and grow sales by pairing Januvia with very widely used compounds that already have proven safety and efficacy profiles, thereby maximizing reach and revenue generated by new products while minimizing the time and money it had to put into extra clinical trials for these products.

- **As a reminder, several other companies currently have or are developing DPP-4 FDCs.** A Galvus/metformin immediate-release FDC (Eucreas) is approved in Europe, an Onglyza/metformin XR (Kombiglyze XR) combination is sold in the US, and an Onglyza/metformin IR combination (Komboglyze) recently received a positive opinion from the European CHMP (see our BMS/AZ 3Q11 earnings at https://closeconcerns.box.net/shared/48f1m9hsmzd3gen7j9az). Several Tradjenta FDC are also being pursued- according to ClinicalTrials.gov, one study (phase 1, ClinicalTrials.gov Identifier: NCT01189201) with a Tradjenta/BI10773 (BI's phase 3 SGLT-2 inhibitor candidate) FDC has been completed while another (ClinicalTrials.gov Identifier: NCT01422876) is in phase 3, one phase 1 study (ClinicalTrials.gov Identifier: NCT01383356) with a Tradjenta/metformin IR combination has been completed while another is ongoing (ClinicalTrials.gov Identifier: NCT01383356), and a phase 1 study (ClinicalTrials.gov Identifier: NCT01276327) with a Tradjenta/pioglitazone combination has been completed.

DPP-4 Fixed-Dose Combinations						
Franchise (Company)	**Metformin-IR Combination**	**Metformin-XR Combination**	**Simvastatin Combination**	**Atorvastatin Combination**	**Pioglitazone Combination**	**SGLT-2 Inhibitor**
Galvus (Novartis)	Available outside the US					
Januvia (Merck)	Available in many markets worldwide	Under FDA review	Available in the US, approvals and launches planned in other markets	Phase 3 publicly disclosed	No longer under investigation	
Onglyza (BMS/AZ)	Received positive CHMP opinion	Available in the US				

	approvals and launches planned in other markets.					
Tradjenta (Boehringer Ingelheim/ Lilly)	Studies publicly disclosed				Studies publicly disclosed	Studies publicly disclosed

- **Positive-trending data regarding the cardiovascular safety of Januvia was highlighted during the call.** Notably, according to company materials, a pooled analysis of 19 double-blind controlled studies of up to two years including more than 10,000 patients and 64 major cardiovascular adverse events (MACE) has shown that the risk for MACE is lower (exposure-adjusted risk ratio 0.68, [95% CI: 0.41, 1.12]), albeit not significantly, with sitagliptin versus comparator treatment. This risk reduction (exposure-adjusted risk ratio 0.76, [95% CI: 0.39, 1.51, again not significant) also holds in analysis of just the placebo-controlled trials included in the original analysis (in which there were a total of 35 MACE). Additionally, a pooled analysis of three sulfonylurea versus comparator studies which will be presented at the International Diabetes Federation Annual Meeting in Dubai in December has suggested a lower cardiovascular risk with sitagliptin than sulfonylurea treatment (0/1269 sitagliptin treated patients vs. 11/1274 sulfonylurea treated patients experienced MACE)-we'll look forward to hearing more about this study's design and implications in December. Finally, the TECOS Trial (ClinicalTrials.gov Identifier: NCT00790205), a currently-recruiting, event-driven phase 3 trial which is enrolling 14,000 patients with type 2 diabetes and a history of cardiovascular disease, is now evaluating the cardiovascular outcomes of long-term treatment with sitagliptin used as part of usual care as compared to usual care without sitagliptin. The trial's primary outcome will be time to first cardiovascular event (up to five years), while its secondary outcomes will include time to all-cause mortality, time to congestive heart failure, and change in renal function (all up to five years). It is expected to complete in December 2014, and we assume we'll hear its results at ADAin the subsequent year. As a reminder, the cardiovascular benefits of a number of other incretins are currently being evaluated in phase 3 trials-exenatide is being evaluated in EXSCEL (five years duration), liraglutide in LEADER (five years duration), and alogliptin in EXAMINE (four years duration). All of these trials are likely to report in the 2013-2016 time frame. While results from initial, small trials have slowly lent clinical weight to previously basic-science-based suggestions of DPP-4's cardiovascular benefits, we'll look to results from these large outcomes trials to better understand these benefits. It may be, of course, that different CVD outcomes are seen with GLP-1 versus DPP-4 inhibitors - we look forward to learning more, as always.
- **Notably, during the call today, management outlined its strategy for maintaining future "leadership" in diabetes**. It noted that in the short term, this strategy includes maintaining leadership in the DPP-4 inhibitor space via development of the once-weekly DPP-4 inhibitor MK-3102 (which it called a "paradigm shift" in diabetes), development of the Januvia/ atorvastatin FDC MK-0431E, completion of TECOs, and seeking approval of Janumet XR in the US. It has additionally pursued maintenance of leadership via its acquisition of SmartCells, which has developed a technology that could result in glucose responsive insulin. We learned during Q&A that the company is merging the preclinical SmartInsulin program with its GlycoFi capabilities (which give it the ability to incorporate glycosylation changes into a protein during expression in yeast rather than through later chemical modification), and that the company's long-term goal is to have both short and long-acting SmartInsulins. While this program is in early stages, management noted it believes it has the potential to be a "game changer." As a reminder, SmartInsulin, is a once-daily glucose-dependent insulin therapy developed at MIT that was licensed to Beverly-MA based

SmartCells from MIT in 2004. In the SmartInsulin formulation, insulin is bound to a biodegradable polymer that includes sugar groups. The insulin-polymer conjugate is coinjected with a multivalent glucose-binding molecule that can attach to the polymer's sugar groups, leading to an aggregate that prevents insulin from entering solution when blood glucose is low. During hyperglycemia, however, glucose binds to the glucose-binding molecule, displacing the insulin-polymer conjugate so that active insulin enters the bloodstream. During in vitro and in vivo studies, SmartInsulin has demonstrated a fast response to glucose challenges and negligible insulin leakage at normal blood glucose levels. Although human studies have not yet begun, SmartInsulin would be administered as a once-daily injection. Merck bought SmartCells in December 2010 (for more details see our December 15, 2010 Closer Look at https://closeconcerns.box.net/shared/27zmahgrj0njh7np5nah)

- **The company's phase 1 diabetes compound MK-1421 was discontinued in late 2010.** The compound's development was suspended when phase 1 graded glucose infusion results showed that very high concentrations of MK-1421 did not provoke insulin secretion. Additionally, Merck has halted investigation of the novel diabetes treatment mechanism that MK-1421 was targeting. Management noted this decision was an example of the early "go-or-no-go" decisions based on biomarkers and modeling/simulation that it hopes to undertake increasingly in the future in order to improve long-term return on investments.

Questions and Answers

Q: The second question is on the DPP-4. Just mechanistically, how do you achieve a week- long inhibition of the DPP-4 enzyme? I understand how it works with bisphosphonates, where you're creating a reservoir of drug in the body. Does this do something like covalent bonding to the enzyme, and is that potentially something that could create a safety issue?

A: In terms of DPP-4, this is another example of our chemists and our biologists just working together to come up with a model. This is not covalent bonding or anything like that. The drug is not metabolized and so it hangs around, and it's not efficiently cleared by the kidney. It hangs around for a week as a molecule, as a free drug. So it's a beautiful story. These are not easy things. I just want to say, making a once-weekly DPP-4 inhibitor was not easy.

Q: I'd like to follow up on the DPP-4. What is the half-life?

A: With respect to the half-life, I don't want to get into half-life. But I just want to emphasize, again, this is a reversible host inhibitor, and as Nancy showed, you're getting very good inhibition for over a week, and so therefore the half-life is very long.

Q: Do you think your R&D franchises in hepatitis C and diabetes are broad and deep enough to sustain the clear commercial momentum that you guys have going? Both disease areas have multiple modalities being developed at this point, where potentially it would require multiple mechanisms, so any thoughts on that? Or do you need to up the game there from an external standpoint?

A: In terms of diabetes, I would say that this is definitely an area where we are going to continue to invest in new mechanisms of action. We think there's still a lot to do with drugs as we move forward. There's some outstanding science that's coming out now in human genetics that's pointing us to new directions that we can go after, where we think we have outstanding opportunities. We see smart insulin as really the next major, huge step-change in the diabetes arena, both for type 1 and type 2. It's early, as Nancy said, but we are making excellent progress preclinically with the smart insulin program. We are merging it with the GlycoFi capabilities we have, where we have the ability to incorporate glycosylation changes into a protein during expression in *Pichia* [*pastoris*, a yeast] as opposed to via chemical modification of the insulin afterwards, and long-term, our goal is to have long-acting as well as short-acting smart insulins that could then be combined with all sorts of things, including some of the devices you are envisioning. And so we really see this as a huge step-change. It's early, but it's a major thing for us to invest in, and so we're going to continue to move forward in both of those directions.

--by Lisa Rotenstein and Kelly Close