CLOSER LOOK

MEMORANDUM

FDA approves Merck/Pfizer's SGLT-2 ertugliflozin under brand name Steglatro; Two FDCs also approved - December 21, 2017

Executive Highlights

- **The FDA has approved Merck/Pfizer's SGLT-2 inhibitor ertugliflozin for type 2 diabetes under brand name Steglatro.** The agency simultaneously approved two fixed-dose combinations: Steglujan (ertugliflozin + sitagliptin - branded separately as Merck's DPP-4 inhibitor Januvia) and Segluromet (ertugliflozin + metformin). This decision came on time with the expected 4Q17, though we were surprised that both companies were delayed in issuing a press release. The FDA-approved Steglatro product label was accessible online earlier this week, and can be found here. Merck/Pfizer finally published a joint press release Friday morning (December 22).
- **Merck/Pfizer have been particularly enthusiastic about the SGLT-2/DPP-4 fixed-dose combination, now branded Steglujan.** Januvia is the clear market leader within the DPP-4 inhibitor class, and we know it's also the highest-prescribed product of all branded diabetes drugs (Merck's Januvia franchise exceeded $6 billion in sales in 2016). We believe the familiarity among real-world HCPs (and to some extent, patients) could help accelerate uptake of Steglujan relative to Glyxambi (Lilly/BI) and Qtern (AZ). There are other problems with the combinations, mostly pertaining to HCPs as we understand it, and we hope that Merck/Pfizer are ready to crush these since we view this and other combos as particularly useful for patients and particularly relevant to use earlier in disease management.
- **Pricing now looms large,** as is to be expected following a new product(s) approval. According to Merck/Pfizer's joint announcement, the monotherapy will cost $8.94/day (less than existing SGLT-2 monotherapies, which cost ~$17/day), while the combo with sitagliptin will cost $17.45/day (slightly less than Glyxambi at ~$22/day). We note that list price only says so much without taking into account patient savings programs and insurance coverage, and reimbursement may be a challenge for Steglatro in 2018 due to timing of the payer contracting cycle (though the lower cost could be a competitive advantage down the line). We'll revisit these cost questions again once we can compare list prices between Steglatro and the other SGLT-2s side-by-side at our local pharmacy - US launch is slated for 1Q18 (Steglatro and Steglujan in January, Segluromet in February).
- **Overall, we see enormous potential for Steglatro to further grow the SGLT-2 class, although CVOT results (VERTIS CV) will have a clear impact.** Expanded patient choice is a clear win (such as it is - there's less and less of this with formularies, but we do think patient awareness of the class will increase with ertugliflozin). With four power players in the SGLT-2 market, perhaps we'll see meaningful improvement in reimbursement for these highly-effective agents. Also of note, Merck is substantially expanding its diabetes portfolio with these three new products, and we imagine the company's experience making Januvia a commercial success bodes well for Steglatro, Steglujan, and Segluromet.

The FDA has approved Merck/Pfizer's SGLT-2 inhibitor ertugliflozin for type 2 diabetes under brand name Steglatro. This positive decision comes on time with the expected 4Q17 (after the companies submitted an NDA in 4Q16), and makes for a four-product SGLT-2 inhibitor class: Steglatro joins Lilly/BI's Jardiance (empagliflozin), J&J's Invokana (canagliflozin), and AZ's Farxiga (dapagliflozin). Neither company issued a timely press release, but the product label for Steglatro was actually accessible online earlier this week. We've

never seen something approved with a product label out there but no press release, and we hope this doesn't bode poorly for the drug's prioritization within these two pharmaceutical behemoths. Of course, Merck/Pfizer did finally post a joint announcement on Friday morning (December 22).

FDA simultaneously approved Steglujan (ertugliflozin/sitagliptin fixed-dose combination) and Segluromet (ertugliflozin/metformin fixed-dose combination). All three products are slated for a 1Q18 US launch (Steglatro and Steglujan in January, Segluromet in February).

Merck/Pfizer have been particularly enthusiastic about the SGLT-2/DPP-4 combination, which showed superior efficacy vs. either monotherapy in VERTIS FACTORIAL and VERTIS SITA2. In VERTIS FACTORIAL, for example, after 52 weeks, ertugliflozin + sitagliptin gave a 1.4% drop in A1c from a baseline of 8.6% vs. a ~1% drop with ertugliflozin alone. Although other products in this class - including Lilly/BI's Glyxambi (empagliflozin/linagliptin) and AZ's Qtern (dapagliflozin/saxagliptin) - have struggled to gain commercial traction, Merck/Pfizer seem ready to invest in order to make Steglujan a success. The other companies haven't necessarily invested less than we expected, but we do think doctors have taken too long to get on board with combos (we see this with basal insulin/GLP-1 combos also). Management from both Merck and Pfizer have alluded to sitagliptin (Merck's Januvia) as a leading drug within the DPP-4 market and within diabetes care more generally (indeed, Januvia is the highest-prescribed branded diabetes medicine today). This familiarity among real-world HCPs/patients would certainly encourage patient switches to the fixed-dose combo, and could help accelerate uptake of Steglujan relative to Glyxambi and Qtern (of course, a similar story was true for Lantus, which hasn't helped drive the basal insulin/GLP-1 class as far as we can tell). We'll be keeping a close eye on these market dynamics in 2018 and beyond.

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Price and Reimbursement

- **Price now looms large.** According to Merck/Pfizer's joint announcement, Steglatro will be priced at $8.94/day (~$268 for a 30-day supply of once-daily tablets) as will Segluromet. We imagine Steglatro is priced slightly lower than existing SGLT-2 options in order to compete. A call to a local Walgreens turned up monthly list prices of $518 (25 mg), $517 (100 mg), and $520 (10 mg) for Jardiance, Invokana, and Farxiga, respectively, which corresponds to cost of ~$17/day. Steglujan will be priced at $17.45/day (~$524/month), given the higher cost to manufacture ertugliflozin and sitagliptin in one tablet. Lilly/BI's Glyxambi is listed at ~$657 for a 30-day supply in the US, or a daily price of ~$22, which is in the same ballpark as standalone Jardiance. AZ's Qtern was FDA-approved in 1Q17, but has yet to launch in US pharmacies. We understand that list price only says so much without taking into account patient savings programs and insurance coverage.
- **Notably, reimbursement for Steglatro, Steglujan, and Segluromet may be a challenge in 2018 given the timing of the payer contracting cycle.** CVS Health announced its 2018 formulary back in August, excluding Lilly/BI's Jardiance in favor of J&J's Invokana, while keeping AZ's Farxiga as a preferred drug.
    - **Regardless, given Merck/Pfizer's strength and expertise commercializing drugs, we expect these ertugliflozin products to be serious contenders in the SGLT-2 inhibitor market.** In our view, expanded patient choice is a clear win, and we see ample opportunity for whole class growth - according to a recent Diabetes Care paper, only 7% of second-line diabetes prescriptions in the US currently go to an SGLT-2 inhibitor, despite the tremendous composite benefit (glucose-lowering, weight loss,

convenient oral administration, no hypoglycemia risk, possible CV/renal protection, etc.). Hopefully, with four power players in the SGLT-2 market, reimbursement for this class will meaningfully improve. We do note, of course, that some HCPs may be worried about the side-effect profile, etc. Indeed, it's telling that Glyxambi is priced in the same ballpark as Jardiance, and yet prescription volume has been low for the fixed-dose combination thearpy - this points to HCP reluctance (in addition to patient concerns, possibly lack of awareness, and likely some reimbursement challenges), and Merck/Pfizer will have to confront this in promoting Steglujan.

The VERTIS Clinical Program

- **Diabetes thought leaders have been optimistic about ertugliflozin from a scientific/ clinical perspective, and ADA's Chief Scientific, Medical, and Mission Officer Dr. Will Cefalu even called out VERTIS studies as a "Best of ADA 2017" highlight.** This year's ADA Scientific Sessions featured several oral presentations and posters on ertugliflozin, including one-year data from VERTIS FACTORIAL (presented by Dr. Richard Pratley), one-year data from VERTIS SITA2 (presented by Dr. Jie Liu), 26-week results from VERTIS SITA, and 52-week results from VERTIS MONO. A meta-analysis of six VERTIS trials was the subject of a poster at IDF, showing consistently greater glucose-lowering, weight loss, and systolic blood pressure reductions with ertugliflozin vs. its comparator. The one exception was VERTIS SU, presented at EASD 2017, in which 15 mg ertugliflozin was non-inferior to SU glimepiride on the primary endpoint of A1c-lowering after 52 weeks.
- **Demonstrating CV benefit will likely be important for Steglatro to compete with other SGLT-2 inhibitors, considering Jardiance is already indicated for the reduction of CV death and J&J has filed for a CV indication to be added to the Invokana label as well.** To this end, the VERTIS CV CVOT is ongoing, expected to complete October 2019. Before that, we'll see results from DECLARE on Farxiga (dapagliflozin), expected in the second half of 2018.
- **Steglatro has been approved with a label warning for lower-limb (and especially toe) amputations, but the language clearly states that this was found with another SGLT-2 inhibitor (Invokana), and that despite a higher frequency of amputations in ertugliflozin-treated groups vs. comparator groups, no causal link has been established between ertugliflozin and amputations.** Data from a large outcomes study (VERTIS CV) will be more telling vs. phase 3. We continue to believe that amputation risk should be manageable in the real world with proper patient education and foot care, and that this concern shouldn't stand in the way of patients benefiting from SGLT-2 inhibitor therapy. We think it's important to mention here that neither Jardiance nor Farxiga have any sort of amputation warning on their current US labels (though the EMA has extended an amputation warning to the entire class), and we'll be curious to see if the warning has any commercial impact for Steglatro.

Close Concerns Questions

Q: How will the reimbursement landscape for SGLT-2 inhibitors change with a fourth market entry?

Q: Could Steglujan be the first SGLT-2/DPP-4 fixed-dose combination to experience significant real-world uptake? How will Merck/Pfizer position the FDC relative to the other products in the ertugliflozin franchise?

Q: What will marketing/commercialization activities look like? We hope to see significant investment, especially as this approval represents an important moment for Merck, becoming an even bigger player in diabetes.

Q: Will VERTIS CV lend additional evidence for a cardioprotective class effect?

Q: Could Merck/Pfizer launch trials of ertugliflozin in heart failure and/or CKD? Based on positive results for heart failure hospitalization and renal endpoints in EMPA-REG OUTCOME and CANVAS, Lilly/BI have launched the EMPEROR HF program for empagliflozin in heart failure, AZ has launched the Dapa-HF study for dapagliflozin in heart failure, and all three existing SGLT-2 drugs are being evaluated in kidney disease.

Q: Why was there a delay in company announcements of this FDA approval?

-- by Payal Marathe and Kelly Close