CLOSER LOOK

MEMORANDUM

J&J submits sNDA for Invokana's CV indication based on CANVAS results - October 2, 2017

Executive Highlights

- Even faster than we expected, J&J has submitted a Supplemental New Drug Application (sNDA) for SGLT-2 inhibitor Invokana (canagliflozin), requesting an expanded indication for reduced risk of adverse CV events, including non-fatal MI, non-fatal stroke, and CV death in adults with type 2 diabetes who have established CV disease or who face high CV risk. This FDA filing comes in time with end of September guidance. Assuming a standard 10-12 month review process, a regulatory decision is expected between August-October 2018.
- The sNDA is based on positive results from the CANVAS trial, presented at ADA 2017.
- If this label update is approved, Invokana will be the second SGLT-2 inhibitor on the market with a CV indication, though Lilly/BI's Jardiance (empagliflozin) is indicated specifically for the reduction of CV death (as opposed to all major CV events). This matches the data seen in EMPA-REG OUTCOME vs. CANVAS. Both CVOTs found a significant 14% risk reduction for three-point MACE (non-fatal MI, non-fatal stroke, and CV death). While the cardioprotection in CANVAS was more evenly distributed across individual components of MACE, though none reached statistical significance on their own, the cardioprotection in EMPA-REG OUTCOME (for Jardiance) was driven by a 38% relative risk reduction for CV death.
- At this point, it's unclear whether FDA will schedule an Advisory Committee meeting to discuss the Invokana sNDA. Precedent suggests yes, since the agency convened Advisory Committees prior to approving CV indications for Jardiance and for Novo Nordisk's GLP-1 agonist Victoza (liraglutide), but we'll have to wait-and-see - the relatively higher amputation risk might also confer a slightly higher chance though presumably the FDA understands more than anyone that this is a very low risk for the entire population and that there is already a black box.

This morning, J&J announced that a Supplemental New Drug Application (sNDA) has been filed with the FDA, requesting a new CV indication for SGLT-2 inhibitor Invokana (canagliflozin) and for fixed-dose combinations Invokamet (canagliflozin/metformin) and Invokamet XR (canagliflozin/metformin extended-release). Based on positive outcomes data from CANVAS - namely, the 14% risk reduction for three-point MACE (non-fatal MI, non-fatal stroke, or CV death) associated with canagliflozin vs. placebo (p=0.0158 for superiority) - the company is seeking an indication for the reduced risk of major adverse CV events. Assuming a standard 10-12 month review period, an FDA decision is expected in late 3Q18 or early 4Q18. At ADA 2017 (where full CANVAS results were presented), we learned from Janssen's Global Head of Cardiovascular & Metabolism Dr. James List that an sNDA would be filed by the end of September - news of the submission comes right on time.

Following positive EMPA-REG OUTCOME results, Lilly/BI filed an sNDA for their SGLT-2 inhibitor Jardiance (empagliflozin) seeking a new indication for the reduced risk of CV death, specifically. This landmark CVOT found a 38% relative risk reduction for CV death with empagliflozin vs. placebo (p<0.0001). The risk reduction for three-point MACE was similar to that in CANVAS at 14% (p=0.038 for superiority), but was driven primarily by the lower frequency of CV death in the Jardiance group. In contrast, all individual components of MACE trended in favor of canagliflozin in CANVAS, but none met the threshold for statistical significance: The hazard ratio for non-fatal MI was 0.85 (95% CI: 0.69-1.05), for non-fatal stroke was 0.90 (95% CI: 0.71-1.15), and for CV death was 0.87 (95% CI: 0.72-1.06). We imagine

both sNDA submissions were data-driven decisions - the 38% risk reduction for CV death in EMPA-REG OUTCOME is particularly striking, while the cardioprotection in CANVAS was more evenly distributed across MI, stroke, and CV death. If approved, we wonder how Invokana's indication pertaining to major adverse CV events will lead to different marketing tactics vs. those used to promote Jardiance's indication pertaining to CV death (granted in December 2016). Notably, Novo Nordisk's GLP-1 agonist Victoza (liraglutide) was recently approved to reduce the risk of major adverse CV events (encompassing MI, stroke, and CV death), and we're just now starting to see commercial rollout of this broader indication.

In our view, this sNDA marks an important step forward for the Invokana franchise and for the SGLT-2 inhibitor class as a whole. Together, EMPA-REG OUTCOME and CANVAS have built a compelling case for a cardioprotective class effect (DECLARE for AZ's dapagliflozin, branded Farxiga, could be the icing on the cake when it reports in 2H18). With a second CV indication within the class, patients with type 2 diabetes could start taking SGLT-2 inhibitor therapy not only to lower their blood glucose, blood pressure, and body weight, but to prevent CV death (which remains the leading cause of death for the diabetes patient population, by far) and adverse CV events more generally. We can hardly contain our excitement about this shift from A1c-centric diabetes care to a real emphasis on outcomes!

Invokana sales were down 23% YOY in 2Q17 to $295 million, following an equally tough 1Q17 when global revenue declined 13% YOY to $284 million. A label update reflecting CV benefit could serve as a much-needed boost to this business - that is, if J&J is able to overcome the negative commercial effects of the boxed warning for lower limb amputations. Indeed, CANVAS found a nearly two-fold risk for lower-extremity amputations with Invokana vs. placebo (HR=1.97, p<0.001), and though base rate of amputations was low, this remains a very visceral complication and is understandably concerning to patients/providers. A post-hoc analysis presented by Dr. Bruce Neal at EASD 2017 highlighted common precipitating events for an amputation in CANVAS: prior amputation, infection, gangrene, peripheral arterial disease, ulcers, acute limb ischemia, and neuropathy. Dr. Neal reinforced that canagliflozin still approximately doubled a person's amputation risk, but we're hopeful that J&J might now lead an initiative to improve patient education around proper foot care in diabetes, an area we think is currently sorely lacking and that we have recently learned is highly addressable. We continue to believe that Invokana's amputation risk will be manageable with careful patient selection and monitoring. That said, we expect it will take some concerted effort on the company's part - separate from pursuing a CV indication - to overcome the commercial challenges stemming from this safety issue.

- **It's unclear whether the FDA will convene an Advisory Committee to discuss Invokana's label update.** We attended Advisory Committees for both Jardiance and Victoza prior to their label revisions, so we wouldn't be surprised if a similar meeting was called for Invokana. We're curious to see how FDA approaches canagliflozin's complicated risk/benefit profile - the impressive 14% risk reduction for three-point MACE on one side, the safety signal for lower limb amputations on the other. While we certainly hope the amputation data doesn't cloud the compelling cardioprotection results, and while some say it may be hard for FDA to look past safety issues until they're satisfactorily resolved, we actually believe that FDA may also well decide this has been addressed very well with the black box. We don't see any reason a CV indication can't be listed alongside the boxed warning for amputations on the Invokana product label, leaving providers to interpret the risk/benefit profile for individual patients (far more people are at high risk of a heart attack or stroke than any kind of amputation, so we don't see this being a deterrent to an updated label). As one example, Dr. Anne Peters shared with us that some of her patients achieve greater A1c-lowering and weight loss on Invokana vs. Jardiance, explaining that she wouldn't switch her patients off Invokana unless they exhibit other risk factors for amputations (i.e. prior amputation, foot ulcers, etc.).
- **Notably, J&J has requested a CV indication extending to the entire canagliflozin family of products, including Invokamet and Invokamet XR.** Lilly/BI similarly filed an sNDA for Jardiance and Synjardy (empagliflozin/metformin), but FDA only granted the indication for reduced risk of CV death to standalone Jardiance. Data from EMPA-REG OUTCOME was added to the Synjardy product label (as well as Synjardy XR and Glyxambi [empagliflozin/linagliptin]), but

this doesn't carry quite the same weight as an official indication. Considering how busy diabetes care providers can be, an expanded indication listed near the top of a product label does more to spur prescriptions than RCT data listed lower down (though the latter is still a key victory, in our book). Just as EMPA-REG OUTCOME assessed standalone empagliflozin only, CANVAS assessed standalone canagliflozin only (though many participants in both trials were on concomitant metformin therapy). We'll be curious to see if FDA takes the same, more conservative approach in evaluating the Invokana sNDA. Interestingly, the EMA seems to be less conservative on this front: The Committee for Medicinal Products for Human Use (CHMP) recently recommended to the EMA that LEADER data be added to the Saxenda product label, even though this CVOT investigated lower-dose liraglutide (branded Victoza for type 2 diabetes) while Saxenda is higher-dose liraglutide (3.0 mg) for obesity. It's hard to imagine FDA approving this label revision.

-- by Payal Marathe and Kelly Close