Closer Look

MEMORANDUM

BREAKING NEWS: EMPA-REG lives up to the hype! 14% risk reduction for MACE, 38% for CV death, 35% for HF hospitalization; topline results - September 17, 2015

The results, (published in the NEJM just moments ago) demonstrate a significant 14% risk reduction for the primary MACE endpoint (CV death, non-fatal MI, and stroke) with Jardiance vs. placebo (HR = 0.86; 95% CI: 0.74-0.99; p=0.04 for superiority). *The improvement was driven by a whopping 38% reduction in CV death (HR = 0.62; 95% CI: 0.49-0.77; p<0.001), as there was no significant difference in the risk of non-fatal MI or non-fatal stroke. As if that weren't impressive enough, Jardiance also led to a 32% reduction in all-cause mortality (HR = 0.68; 95% CI: 0.57-0.82; p<0.001) and a 35% reduction in hospitalization due to heart failure (HR = 0.65; 95% CI: 0.50-0.85; p=0.002) . In addition, the separation between the Kaplan-Meier curves for all-cause and CV mortality and hospitalization for heart failure appeared to be increasing toward the end of the trial, suggesting that the benefits could become even more significant over time - that had been a big question of ours. Notably, there was no significant difference between the 10 mg and 25 mg doses of Jardiance. As Lilly/BI's announcement emphasized, these improvements occurred in the context of a high-risk population (almost all participants had existing cardiovascular disease) receiving standard of care for diabetes and cardiovascular disease, including blood pressure and lipid-lowering medications for the vast majority of patients. Jardiance's safety profile was consistent with that seen in previous trials; importantly, the incidence of ketoacidosis was ≤0.1% and comparable across treatment groups. There were also no imbalances in bone fracture risk.*

It goes without saying that these results are an enormous win for the diabetes community and figure to have a profound impact on the standard of care for type 2 diabetes going forward - especially in high-risk patients. Jardiance is the first diabetes drug to demonstrate cardioprotection in a robust, dedicated outcomes trial (involving over 7,000 patients and 772 events), and the magnitude of the positive results (at the higher end of our team's predictions) suggest that there should be few questions about their conclusiveness. Our money is on blood pressure reduction as the primary driver of the improvements considering the demonstrated strong relationship with CV outcomes, though weight loss and improvements in HDL cholesterol and triglycerides could have contributed as well. We expect that the results are likely indicative of an SGLT-2 inhibitor class effect given the homogeneity of the class, but this trial specifically tests Jardiance and reflects Jardiance data - we do think they should certainly help Jardiance pick up some steam vs. its competitors. As a reminder, the other SGLT-2 inhibitor cardiovascular outcomes trials (CVOTs) report results in 2017 for J&J's Invokana (canagliflozin) and in 2019 for AZ's Farxiga (dapagliflozin). If results from those trials are positive as well, SGLT-2 inhibitors could very well become the standard second-line therapy for type 2 diabetes, or perhaps even first-line once they are generic (or first line for patients with high risk of CV disease who are good advocates). We will also look forward to seeing results for J&J's Invokana and potential renal protection. Read on below for some of our remaining questions about these results and their implications, and we will be back soon with extensive coverage of the full results presentation.

Close Concerns Questions

- Were the results consistent across all subgroups, including more recently diagnosed patients?
- What were the primary mechanistic drivers of the results?
- Was the reduction in CV death driven by a reduction in heart failure risk?
- Were there improvements in albuminuria?

- When will these results be added to Jardiance's label?
- To what extent will patients, clinicians, and payers assume these results are indicative of an SGLT-2 inhibitor class effect?
- How much will these results boost the SGLT-2 inhibitor class relative to the DPP-4 inhibitor class? How much of a factor will the heart failure results be?
- Will these results enable stronger reimbursement for Jardiance?
- Will investors lobby Lilly/BI to raise the price for Jardiance based on these results?
- Will the results help Glyxambi (empagliflozin/linagliptin) pick up steam after an initial slow start?
- How much reassurance will these results provide about the risk of ketoacidosis with SGLT-2 inhibitors in type 2 diabetes?
- Will SGLT-2 inhibitors become the standard second-line therapy for type 2 diabetes?
- Do these results increase optimism that trials of GLP-1 agonists will also be able to demonstrate cardioprotection?
- What implications do these results have for the prospects for SGLT-2/GLP-1 combinations?
- How will these results influence the debate over the costs and benefits of the 2008 FDA CV Guidance? (can we link to this? Weirdly I can't find it in CCKB - any thought where this is?)

-- by Emily Regier, Helen Gao, and Kelly Close