CLOSER LOOK

MEMORANDUM

Novo Nordisk requests label update for Victoza (liraglutide) LEADER cardioprotection in Supplemental New Drug Application - October 25, 2016

Executive Highlights

- Today, Novo Nordisk filed a Supplemental New Drug Application (sNDA) with the FDA and a Type II Variation application with the EMA, petitioning to include positive cardiovascular outcomes data from the LEADER trial on the label for GLP-1 agonist Victoza (liraglutide).

Novo Nordisk announced today that the company has submitted a Supplemental New Drug Application (sNDA) to the FDA to include data from the LEADER trial on the label for GLP-1 agonist Victoza (liraglutide). The company also filed a Type II Variation application with the EMA detailing the same request. The revised label would reflect the impressive cardioprotective benefit demonstrated in LEADER, including the 13% reduced risk for three-point MACE (non-fatal MI, non-fatal stroke, and CV death) primary endpoint and the 22% reduced risk for cardiovascular (CV) death, which was the most robust CV effect observed in the trial. Assuming a standard 10-month review period, an FDA decision is expected by August 2017. This is an exciting next step for Victoza and for type 2 diabetes patients at high-risk for CV events, as we expect this label update - if approved - will cause upswing in the drug's prescriptions and sales, and will be helpful in spreading awareness of the drug's potential cardioprotective benefit to busy patients and HCPs.

In our view, the potential for the inclusion of positive CV data on drug labels is an extremely important incentive for pharmaceutical companies working in diabetes. A CVOT, required by the FDA's 2008 guidance, is a tremendous investment of time and money. Drugs that show superiority in cardioprotection (or renal protection) would be immensely beneficial to people with diabetes (even just the sub-groups studied), and a label revision is a critical intermediate step that bridges the gap between research and real-world patients and providers by allowing the results to be broadly publicized and leveraged in formulary access negotiations.

- **It's unclear at this point if the FDA will require a dedicated Advisory Committee meeting to discuss a Victoza label update,** as was the case for Lilly/BI with the proposed indication expansion for SGLT-2 inhibitor Jardiance (empagliflozin) and Synjardy (empagliflozin/metformin) based on the EMPA-REG OUTCOME trial. The vote at Lilly/BI's Advisory Committee was a very close 12-11 in favor of label change, which many leaders in the diabetes field have criticized as excessively conservative. Perhaps Dr. Neil Poulter put it best at EASD 2016: "One excuse at the Jardiance Advisory Committee was 'we're not quite sure about the mechanism' - who cares?! While I applaud conservatism, it's time to take action." Indeed, the FDA delayed its decision on a Jardiance label update by 90 days, and there's a chance that Victoza may face similar challenges following the sNDA submission. Our ears are peeled for more information on this filing and what's to come for the Victoza label. Novo Nordisk reports its 3Q16 earnings this Friday, October 28 - we'll of course be listening for additional commentary on LEADER and the sNDA. While we're also curious to see how the trial results may have impacted Victoza sales in 3Q16, we believe this won't have been much, since data were published with only three weeks left in the 2Q16 quarter, and since there is not yet a label change.
- **Conversation on both LEADER and EMPA-REG OUTCOME has been running high at recent conferences, and we've noticed a diverging of opinions between cardiologists and endocrinologists.** Dr. Leslie Cho pointed out at the Jardiance Advisory Committee that all cardiologists on the panel voted 'yes,' in support of a revised label. We heard at ESC 2016 that

cardiologists are resoundingly excited about the CV benefit of empagliflozin (and have been far less conservative in recommending empagliflozin in their guidelines compared to AACE). In contrast, Dr. George Bakris noted at CMHC 2016 that endocrinologists are more comfortable with the LEADER results. He attributed this to our more fleshed-out understanding of liraglutide's mechanism of cardioprotection - the dominant thinking is that the agent exerts an atherosclerotic effect.

-- by Payal Marathe, Helen Gao, and Kelly Close