CLOSER LOOK

MEMORANDUM

LEADER shows 13% risk reduction for primary MACE endpoint with Novo Nordisk's Victoza (liraglutide) and 22% risk reduction for CV death - June 13, 2016

Executive Highlights

- Results from the LEADER trial, just presented at ADA and published in the NEJM, demonstrated a significant 13% risk reduction with Novo Nordisk's Victoza (liraglutide) vs. placebo (HR = 0.87; 95% CI: 0.78-0.97; p=0.01) for the primary endpoint of three-point MACE (non-fatal MI, non-fatal stroke, and CV death).
- The benefit was driven primarily by a significant 22% risk reduction for CV death (HR = 0.78; 95% CI: 0.66-0.93; p=0.007), though all three components contributed.
- The results also demonstrated a significant 22% reduction in adverse renal outcomes with Victoza (HR = 0.78; 95% CI: 0.67-0.92; p=0.003).
- The results on total microvascular outcomes and hypoglycemia were also particularly notable and we will be expanding this report soon to discuss this.

Results from the LEADER trial, just presented at ADA and published in the NEJM, demonstrated a significant 13% risk reduction (HR = 0.87; 95% CI: 0.78-0.97; p=0.01) for the primary three-point MACE endpoint (non-fatal MI, non-fatal stroke, and CV death) with Novo Nordisk's Victoza (liraglutide) vs. placebo, both in addition to standard of care. Results for an expanded MACE composite endpoint (including coronary revascularization and hospitalization for unstable angina or heart failure) were consistent with the primary results, demonstrating a significant 12% risk reduction with Victoza (HR = 0.87; 95% CI: 0.81-0.96; p=0.005).

Novo Nordisk's topline results announcement in March and the slides shown during a press conference yesterday noted that the risk reduction was derived from all three components of MACE, but the largest contribution appeared to come from the significant 22% risk reduction for CV death (HR = 0.78; 95% CI: 0.66-0.93; p=0.007); all-cause mortality was also reduced by 15% (HR = 0.85; 95% CI: 0.74-0.97; p=0.02). The point estimates for non-fatal MI and non-fatal stroke trended in the right direction, but the results did not reach statistical significance. The hazard ratio for non-fatal MI was 0.88 (95% CI: 0.75-1.03; p=0.11) and the hazard ratio for non-fatal stroke was 0.89 (95% CI: 0.72-1.11; p=0.30). There was also a significant 16% risk reduction (HR = 0.84; 95% CI: 0.73-0.97; p=0.02) for the composite microvascular endpoint driven by a 22% risk reduction for adverse renal events (HR = 0.78; 95% CI: 0.67-0.92; p=0.003). The results for hospitalization for heart failure were neutral but trended in the right direction (HR = 0.87; 95% CI: 0.73-1.05; p=0.14). We were particularly moved to see the significantly lower hypoglycemia associated with liraglutide; although this isn't new news, seeing over 20% less hypoglycemia experienced by people in this trial was very moving. See below for more details on the study design and other results. We were very pleased to hear there was no increase in pancreatitis though there was an increase in gallstones.

While there will be plenty of time for speculation about the mechanism of benefit in the next few months, the (very) early consensus seems to be that this was likely an atherosclerotic effect. In the NEJM paper, the authors contrasted these results with the positive EMPA-REG OUTCOME results for Lilly/BI's Jardiance (empagliflozin), noting that the benefit in LEADER took longer to emerge and the effects on the individual components of the primary endpoint were more consistent. While acknowledging that the differences could have been due to chance or to differences in the patient population, they suggested that the EMPA-REG OUTCOME results were more consistent with a hemodynamic effect and the LEADER results with an

atherosclerotic effect. The investigators echoed this hypothesis in our recent conversations with them but added that an atherosclerotic benefit could have resulted from either indirect effects on weight/blood pressure/glucose or from direct effects on the heart or blood vessels. While they urged that direct comparisons between LEADER and EMPA-REG OUTCOME should not be made, they nonetheless emphasized that the timing and pattern of events in the two trials appears to be different, with LEADER demonstrating a more gradual benefit and more consistency across outcomes. We were pleased to hear the investigators emphasize that these results apply to patients at high risk of CV events receiving standard of care and we look forward to learning over time how generalizable the very impressive results are. See the end of this document for more discussion from KOLs and Q&A. We will expand this report in the next 24 hours and will include it in our ADA Day #4 coverage that we plan to publish on June 14.

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- **LEADER enrolled 9,340 patients with type 2 diabetes and high CV risk.** Patients were eligible for the trial if they had an A1c ≥7% and were either at least 50 years old with established cardiovascular disease or renal failure or at least 60 years old with risk factors for cardiovascular disease. Patients were randomized 1:1 to receive either Victoza or placebo once daily in addition to standard of care. Physicians were instructed to treat patients to target for A1c, blood pressure, and lipids and were allowed to use any diabetes medications except for GLP-1 agonists, DPP-4 inhibitors, or pramlintide. At baseline, participants had a mean age of 64 years, mean diabetes duration of 12.8-12.9 years, mean A1c of 8.7%, and mean BMI of 32.5 kg/m^2.
- **Victoza produced modest but sustained reductions in A1c, weight, and systolic blood pressure and a modest increase in heart rate.** Because the goal was to assess non-glycemic effects of Victoza on CV outcomes, the investigators aimed to minimize A1c differences between the groups by treating all patients to a target of 7%. Consistent with this approach, the difference in A1c between the groups shrank over time as use of other diabetes medications increased in the placebo group, but there was still a significant 0.4% difference in favor of Victoza after 36 months ($p<0.001$). Victoza also led to a significant 2.3 kg weight benefit ($p<0.001$) and a significant 1.2 mmHg reduction in systolic blood pressure ($p<0.001$) vs. placebo at 36 months, all of which could have contributed to the benefit for the primary endpoint. Victoza also led to a significant 3.0 bpm increase ($p<0.001$), consistent with previous trials.
- **Adverse event rates were consistent with previous GLP-1 agonist trials, with no signal of increased risk for pancreatitis or pancreatic cancer.** There was no significant difference between the groups in overall adverse event rates; the 1.5% numerical increase in the Victoza group was primarily due to nausea. There were numerically fewer pancreatitis events in the Victoza group (18 vs. 25 events), though there was a significant increase in acute gallstone disease (145 vs. 90 events; $p<0.001$). Hypoglycemia was significantly reduced with Victoza, likely due to greater use of insulin and sulfonylureas in the placebo group. There was a numerical imbalance in pancreatic cancer in favor of placebo (13 vs. 5 events), though Dr. John Buse (UNC, Chapel Hill, NC) noted during the press conference that four additional cases of pancreatic cancer in the placebo group were adjudicated after the patients had died, bringing the total tally to 13 vs. 9 events.

Close Concerns Questions

Q: What was the mechanism of benefit? Was it atherosclerotic? Was it a direct effect on the heart or blood vessels or an indirect effect of the reductions in weight, glucose, and systolic blood pressure?

Q: How generalizable are the results to other patient populations? Will they ultimately apply to people with type 2 diabetes at lower risk of cardiovascular disease? To people with high CV risk without diabetes? To people with type 1 diabetes?

Q: Is the benefit a class effect? Was the difference between the LEADER and ELIXA results due to differences in trial design or intrinsic drug-specific effects? How will any commercial benefit be split between Victoza vs. the GLP-1 agonist class as a whole?

Q: What kind of label update will the data support?

Q: How will marketing change in light of this data (education on GLP-1 and Victoza, pricing, etc.)?

Q: How will guidelines committees incorporate these results and those from EMPA-REG OUTCOME?

Q: How will this influence drug development - how much higher is the bar?

Q: With inevitable comparisons to EMPA-REG OUTCOMES, what will the conclusions be?

Q: Does this increase the opportunity that an outcomes trial using GLP-1 and SGLT-2s will be considered?

Q: How will the results impact Novo Nordisk's obesity drug Saxenda?

Discussion from ADA Press Briefing on LEADER

Dr. Robert Eckel (University of Colorado, Aurora, CO): We think lower glucose is better for you because of microvascular disease. A meta-analysis of the trials involving intensification of insulin says there's a 10% benefit on CV outcomes but also additional risks. Many people can't achieve good A1cs and there's more severe hypoglycemia. That doesn't mean we shouldn't manage better with insulin because microvascular outcomes are clearly improved.

Most of us agree that metformin is the drug of choice for type 2 diabetes. We've heard at this meeting that it may have pleiotropic effects on cancer and beyond. Now with EMPA-REG and LEADER we have to think beyond metformin to what the second drug of choice might be. The absence of hypoglycemia with liraglutide is impressive. There was actually protection because there was presumably more insulin intensification in the placebo group.

Is this a class effect? Validation is incredibly important. There are studies ongoing with other SGLT-2 inhibitors to validate EMPA-REG. With LEADER, we already have a hint that maybe another drug [semaglutide] is beneficial. It's my understanding that the data will be presented at EASD.

Why is there a benefit? In EMPA-REG, many things were modified in a modest but favorable way. LEADER was similar: lower blood pressure, weight, waist circumference, the lipid data look favorable. Everything is changing modestly in the right direction. Is it the modest A1c reduction or some composite model where everything is additive? That's true of EMPA-REG and LEADER.

Q: What was the number needed to treat?

Dr. John Buse (UNC, Chapel Hill, NC): The number needed to treat for MACE is in the 60s. For death it's in the 90s to low 100s.

Q: Do you think the benefit was more likely due to a direct effect on the heart or blood vessels or to the indirect effects you mentioned?

Dr. Bernard Zinman (Lunenfeld-Tanenbaum Research Institute, Toronto, Canada): This is a new space in diabetes management. These are therapies that we know are effective, and now they have added value. SGLT-2 inhibitors and GLP-1 agonists are clearly different; their mechanisms of lowering glucose are different. With SGLT-2 inhibitors, the pathophysiology starts at the kidney, so the effects are likely mediated through the kidney effect. GLP-1 agonists are very different. There are GLP-1 receptors on the heart and in other parts of the body. We don't know if it's a direct effect or an indirect effect leading to better outcomes.

Dr. Steven Marso (UT Southwestern, Dallas, TX): LEADER is not the type of trial that will clarify the mechanism. It clearly clarifies the magnitude and sustainability of the benefit. Preclinical work suggests some mechanisms, maybe some related to weight, blood pressure, or glycemic control. There's interesting data looking at ischemia reperfusion and work looking at plaque stabilization. If you look at the Kaplan Meier curves from a cardiologist's perspective - and this is pure speculation - it looks like atherosclerosis is a plausible mechanism, with prevention of coronary artery disease progression. We don't know the mechanism but preclinical studies suggest plausible hypotheses.

Q: One prior study with lixisenatide was neutral. Can you comment on the differences in the patient populations? It looks like there is a class difference.

Dr. Buse: Lixisenatide is a very different molecule. The patient population was also different, post-ACS. I think those are the two possibilities. Lixisenatide doesn't provide 24-hour coverage. It has a short half-life with GLP-1 activity for 9-12 hours. Liraglutide provides 24-hour coverage. But it's impossible to tell.

-- by Emily Regier and Kelly Close