CLOSER LOOK

MEMORANDUM

Novo Nordisk announces topline SUSTAIN 6 results demonstrating a cardioprotective benefit for semaglutide - April 28, 2016

Executive Highlights

- Novo Nordisk announced positive topline results from the SUSTAIN 6 CVOT showing that treatment with semaglutide significantly reduced the risk of the primary three-point MACE endpoint (cardiovascular death, non-fatal MI, and non-fatal stroke).
- Novo Nordisk plans to submit semaglutide to regulatory authorities in the US and EU in 4Q16.

Early this morning, Novo Nordisk announced positive topline results from the SUSTAIN 6 cardiovascular outcomes trial (CVOT), designed as a non-inferiority trial, demonstrating a significant cardioprotective benefit for its once-weekly injectable GLP-1 agonist semaglutide. The trial (n=~3,300) found that treatment with semaglutide significantly reduced the risk of the primary three-point MACE endpoint (cardiovascular death, non-fatal MI, and non-fatal stroke). The announcement did not share the hazard ratios or confidence intervals for the relative risk reduction of the composite endpoint or of any of its components. We would imagine that all three components likely contributed to the overall composite risk reduction, as this was the case with the positive LEADER results for Novo Nordisk's other GLP-1 agonist Victoza (liraglutide) - from our view, it reinforces the validity and the importance of those results. Novo Nordisk's Chief Scientific Officer Dr. Mads Thomsen noted during a media call that these data confirmed what they already knew, mainly that semaglutide is more efficacious than other products especially when you look at glucose control, weight management, and cardiovascular effect.

We'll be very interested to see how the relative risk reduction in SUSTAIN 6 compares to that in LEADER - trials thus far have indicated that semaglutide has greater intrinsic efficacy than liraglutide so we would imagine the cardioprotective benefit of semaglutide would at least match, if not exceed, that of liraglutide. That's pretty great as adherence may well be better with the once-weekly, though that is speculation. In terms of safety and tolerability, the announcement characterized the SUSTAIN 6 results as consistent with previous findings. Details on the data were sparse; unfortunately, the full results will not be ready in time for ADA 2016 in June. However, the company has already announced that the full LEADER results will be presented Monday afternoon at ADA. Boy is that session going to be packed!

Novo Nordisk plans to submit semaglutide for regulatory review in the US and EU in 4Q16. Assuming a standard review cycle, semaglutide would likely be approved toward the end of 2017 and launch in 2018. This would presumably allow time for semaglutide's sales to ramp up before current market leader Victoza loses patent exclusivity in 2023. SUSTAIN 6 is the final study in the six-trial SUSTAIN phase 3 development program for semaglutide, and with the full portfolio available, Novo Nordisk is assured that they will have the best in class with semaglutide. Previously, semaglutide has demonstrated impressive A1c and body weight reductions vs. placebo (SUSTAIN 1), Merck's Januvia (sitagliptin, SUSTAIN 2), AZ's Bydureon (exenatide once-weekly, SUSTAIN 3), and Sanofi's Lantus (insulin glargine, SUSTAIN 4). In addition, SUSTAIN 5 demonstrated superior A1c reductions, weight loss, and insulin dose reductions with semaglutide vs. placebo as an add-on to basal insulin. We imagine that Novo Nordisk could eventually co-formulate semaglutide with a basal insulin such as Tresiba (insulin degludec), creating a "next-generation" version of Xultophy (insulin degludec/liraglutide).

- **We are very interested in what the A1c and body weight reductions were in SUSTAIN 6.** When the LEADER results were announced, Dr. Mads Thomsen suggested that they may have been driven by a combination of effects on glucose, weight, and blood pressure. We found this rather surprising, as we had assumed that LEADER, like other CVOTs, would aim for "glycemic equipoise"

between groups to reveal any non-glycemic cardiovascular effects. Previous results have indicated that semaglutide has greater glucose-lowering efficacy than liraglutide, as well as a greater effect on body weight, so we are curious to see whether these effects could have contributed to an even greater cardioprotective benefit. We're also curious what the rate of adverse events was in the trial, particularly for nausea and other GI side effects. SUSTAIN 3 demonstrated nausea rates that were twice as high rate with semaglutide vs. Bydureon (22% vs. 11%), and we wonder what impact this might have on semaglutide's uptake.

- **Semaglutide is the second GLP-1 agonist and third diabetes drug to demonstrate a cardioprotective benefit in a dedicated outcomes trial (all within less than a year!).** EMPA-REG OUTCOME demonstrated a cardioprotective benefit, likely driven by a benefit on heart failure, for Lilly/BI's SGLT-2 inhibitor Jardiance (empagliflozin) last year. Topline results from LEADER indicated a cardioprotective benefit driven by reductions in cardiovascular death, MI, and stroke for Novo Nordisk's Victoza. The positive LEADER results contributed to great optimism that the SUSTAIN 6 results would also demonstrate a cardioprotective benefit. The SUSTAIN 6 results solidify semaglutide's position as a successor to Victoza and have very positive implications for the GLP-1 agonist class a whole, though Novo Nordisk emphasized that the CV outcomes results for the class overall have been mixed (neutral results for Sanofi's Lyxumia [lixisenatide] in ELIXA). According to Dr. Mads Thomsen, while we do not know for certain if this is a class effect, what we do know is that the acylated class of GLP-1s (liraglutide and semaglutide) is showing a positive benefit. Intarcia's potentially transformative ITCA 650 implantable exenatide mini-pump is expected to report CVOT results soon as well. If that trial is positive as well, we imagine we would see even greater adoption of the GLP-1 agonist class, especially if Intarcia proceeds with its current plans to price ITCA 650 at a relatively lower price-per-unit compared to other GLP-1 agonists. The GLP-1 agonist class as a whole has already seen a significant rebound over the last year, even before the announcement of the topline LEADER and SUSTAIN 6 results. According to Lilly's 1Q16 update, the overall class experienced a 30% growth by volume - we imagine this will only increase going forward. Our impression is that restrictions from payers often prevent this class from being used early in the progression of type 2 diabetes, and we expect that these results could significantly change that equation, at least for high-CV risk patients.
- **Novo Nordisk also recently initiated an open-label phase 3 head-to-head trial of semaglutide and Lilly's Trulicity (dulaglutide).** The trial (n=1,196 patients with type 2 diabetes) has a primary endpoint of change in A1c after 40 weeks and secondary endpoints of change in body weight, fasting plasma glucose, blood pressure, and patient-reported outcomes from baseline and the percentage of patients with an A1c ≤6.5% at the end of the trial. According to ClinicalTrials.gov, the trial is expected to complete in May 2017, and according to Novo Nordisk, the data are expected to be available at the time of launch. The patient-friendly Trulicity (designed in part by IDEO) is the newest GLP-1 agonist on the market and has experienced a very strong launch trajectory; it is now the second most-prescribed GLP-1 agonist according to Lilly's 1Q16 update with 17% of the total prescription [TRx] share in the US. If semaglutide can demonstrate a clear edge over Trulicity in this trial, it would be a major boost to Novo Nordisk's attempts to position its product as a new best-in-class agent with patients, providers, and payers.
    - **We have yet to see a head-to-head trial of semaglutide vs. an SGLT-2 inhibitor.** Especially in light of the EMPA-REG OUTCOME results and the class' marked effect on weight loss, we imagine that a trial between the two agents would be particularly informative for patients and providers. That said, the phase 3 PIONEER program for the oral formulation of semaglutide includes a head-to-head trial with empagliflozin. We expect oral semaglutide will become a more direct competitor to Jardiance than injectable semaglutide, as Novo Nordisk hopes to position the oral version earlier in the diabetes treatment algorithm. GLP-1 agonist/SGLT-2 inhibitor combination therapy is also looking more and more appealing in light of these positive results..

- **Novo Nordisk clearly sees the semaglutide molecule as a very versatile product, in terms of both dosing flexibility and potential wider indications.** Most notably, Novo Nordisk has advanced a once-daily oral formulation of semaglutide into phase 3 with the extensive 10-trial, >9,300 patient PIONEER program. The more patient-friendly delivery could help Novo Nordisk push GLP-1 agonist therapy earlier in the diabetes treatment algorithm and increase the overall use of the class. The company has also initiated a phase 2 trial in type 2 diabetes investigating a variety of once-daily doses of semaglutide vs. liraglutide and placebo. Coupled with the candidate's greater intrinsic efficacy, once-daily dosing could provide steadier concentration and therefore offer better coverage and fewer peak-related side effects compared to once-weekly administration. Outside of type 2 diabetes, Novo Nordisk has also initiated a phase 2 trial for semaglutide in obesity and plans to initiate a trial in NASH. The phase 3 PIONEER program for the oral formulation includes a CVOT and we'll be interested to see if the cardioprotective benefits demonstrated in SUSTAIN 6 extend to the oral version, given the bioavailability challenges associated with oral delivery.
    - **It's unclear if Novo Nordisk will be required to conduct a CVOT for a potential once-daily injectable formulation or for formulations targeted toward obesity or NASH.** Our guess is that a second trial would not be required, but we also imagine any sort of cardiovascular claim on the label for the once-weekly injectable version would not automatically extend to these additional formulations. It is possible that Novo Nordisk would voluntarily undertake additional CVOTs to maximize the potential for differentiation, but at first glance, we would be a bit surprised if they did so, as CVOTs are very expensive to conduct and there is less competition in the obesity and NASH fields. That said, a positive CVOT may make payors much more friendly.

Close Concerns Questions

Q: What was the hazard ratio and confidence interval for the composite three-point MACE endpoint?

Q: What were the hazard ratios and confidence intervals for cardiovascular death, non-fatal myocardial infarction, and non-fatal stroke separately?

Q: Was the relative risk reduction significant for each individual component of the endpoint?

Q: Did semaglutide have a greater effect on one component of the three-point MACE than the others?

Q: What was the impact of semaglutide on heart failure?

Q: How does the relative risk reduction of semaglutide compare to liraglutide? To empagliflozin?

Q: How does the patient population of SUSTAIN 6 compare to that of LEADER? EMPA-REG OUTCOME? ELIXA? To the DPP-4 inhibitor CVOTs?

Q: What might be driving the lack of cardioprotective benefit for Sanofi's ELIXA (lixisenatide) compared to semaglutide and Victoza?

Q: Does the cardioprotective benefit of semaglutide extend to individuals at lower risk of cardiovascular events?

Q: How might these results affect how other formulations of semaglutide might be viewed (oral, once-daily, for obesity, for NASH)?

Q: Could these results influence a decision to develop semaglutide for type 1 diabetes?

Q: What kind of label could the data support?

Q: Will some patients prefer to take semaglutide and Tresiba separately over the Xultophy (insulin degludec/liraglutide) combination?

Q: Will we see efforts to develop an SGLT-2 inhibitor/GLP-1 agonist combination?

Q: Lilly/BI initiated a trial of empagliflozin in patients with heart failure without diabetes. Could we see a similar move from Novo Nordisk for semaglutide?

Q: How will payers view this data when semaglutide is available on the market? Does semaglutide offer a convincing enough additional value proposition on top of Victoza, given that Victoza also demonstrated a cardioprotective benefit? What about ITCA 650?

Q: To what extent will these results drive overall class growth vs. a specific benefit for semaglutide?

Q: How will these results influence pricing for semaglutide?

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