Closer Look

MEMORANDUM

## Novo Nordisk announces positive topline phase 3a results for semaglutide vs. AZ's Bydureon (exenatide once weekly) - September 29, 2015

**Executive Highlights**

- Novo Nordisk announced positive topline results late last week from the SUSTAIN 3 phase 3a trial demonstrating superior A1c reductions (1.5% vs. 0.9%; baseline = 8.4%) and weight loss (5.6 kg vs. 1.8 kg; baseline = 96 kg) with semaglutide compared to AZ's Bydureon (exenatide once weekly).

*Novo Nordisk announced positive topline results late last week from SUSTAIN 3, the second phase 3a trial for its once-weekly GLP-1 agonist semaglutide. The randomized, open-label trial (n = 813 patients with type 2 diabetes) demonstrated significantly greater A1c reductions (1.5% vs. 0.9%; baseline = 8.4%) with 1.0 mg semaglutide vs. AZ's Bydureon (exenatide once weekly) in addition to one or two oral agents after 56 weeks. In addition, a significantly greater percentage of the semaglutide group achieved an A1c <7% at the end of the trial (66% vs. 40% with Bydureon). Semaglutide also produced significantly greater weight loss than Bydureon: 5.6 kg (~12.3 lbs) vs. 1.8 kg (~4.0 lbs) from a baseline of 96 kg (~212 lbs) - we found this surprising and wonder if the same results would be seen in real life. Semaglutide appeared to be safe and well tolerated in the trial, though on a negative note for Novo Nordisk, the rate of nausea was twice as high with semaglutide compared to Bydureon (22% vs. 11%). The overall discontinuation rate due to adverse events was slightly higher with semaglutide than Bydureon but fairly low overall (9.4% vs. 7.2%) and we believe they would be higher in real life since in randomized clinical trials, endos always seem to be able to manage nausea (with the help of educators) better than on average in real life.*

*These positive results are consistent with the expectation that semaglutide would offer greater glycemic efficacy and weight loss compared to existing GLP-1 agonists, though we would have loved to see a direct comparison to Novo Nordisk's current market leader Victoza (liraglutide) or Lilly's user-friendly once-weekly GLP-1 Trulicity (dulaglutide) as well. SUSTAIN 3 is the only one of the six phase 3 semaglutide trials to evaluate only the higher 1.0 mg dose, and we are eager to understand from the other trials whether the 0.5 mg dose can offer less nausea without a significant loss of efficacy. In the SUSTAIN 1 trial vs. placebo (topline results reported in July), both doses of semaglutide produced comparable ~1.5% A1c reductions, though weight loss was greater with the higher dose. The topline results announcement stated only that rates of nausea were comparable to those in similar trials of Victoza and that they diminished over time. We are excited to see data from this extensive phase 3 program continue to arrive over the next six months or so - the next trial to report results should be SUSTAIN 4 against Sanofi's Lantus (insulin glargine). If the current timeline holds, we would expect FDA approval in late 2016 or early 2017. The remaining trials should provide a good sense of semaglutide's profile compared to other type 2 diabetes drug classes and its best position in the treatment algorithm, though we are disappointed that there are no trials evaluating semaglutide against or in combination with an SGLT-2 inhibitor - we also understand that as various options proliferate for patients, it's a lot to ask that so many combinations be tested against each other. Assuming results continue to be positive, this product should certainly help Novo Nordisk maintain its leadership within an increasingly crowded GLP-1 agonist class - we think the availability of semaglutide should expand uptake of the class as a whole.*

- **Novo Nordisk recently announced its decision to advance an oral formulation of semaglutide into phase 3.** The phase 3 PIONEER program, similar to the SUSTAIN program, will consist of seven trials and enroll approximately 8,000 patients. The first study, slated to begin in 1Q16, will evaluate three doses of oral semaglutide (3 mg, 7 mg, and 14 mg) vs. Merck's DPP-4

inhibitor Januvia (sitagliptin). The remaining six trials will be initiated in 2016 and include a CVOT. This product could have significant disruptive potential if the challenges around dosing and bioavailability are overcome; the possibility of future fixed-dose combinations with an SGLT-2 inhibitor is also very exciting.

- **Novo Nordisk suggested in 1Q15 that phase 2 dose-ranging trials of semaglutide in obesity could begin around the time of an approval in diabetes.** Brain scan findings have supported the possibility of greater weight loss with semaglutide than liraglutide, which would also place the drug ahead of all other existing obesity drugs in terms of efficacy, though the side effect profile would be an important consideration. Novo Nordisk also suggested in 1Q15 that any plans for semaglutide in obesity would be independent of Saxenda's (liraglutide 3.0 mg) commercial success, consistent with previous statements emphasizing the company's overall commitment to obesity rather than an exclusive focus on Saxenda.

**Table 1: SUSTAIN phase 3 trial program for semaglutide**

| Trial | Estimated Enrollment | Comparator/Design | Estimated Primary Completion Date | Status |
|---|---|---|---|---|
| SUSTAIN 1 | 390 | Placebo | May 2015 | Topline results reported July 2015 |
| SUSTAIN 2 | 1,200 | Merck's Januvia (sitagliptin) | October 2015 | Ongoing |
| SUSTAIN 3 | 813 | AZ's Bydureon (exenatide) | July 2015 | Topline results reported September 2015 |
| SUSTAIN 4 | 1,089 | Sanofi's Lantus (insulin glargine) | September 2015 | Completed |
| SUSTAIN 5 | 397 | Placebo; add-on to basal insulin and/or metformin | November 2015 | Ongoing |
| SUSTAIN 6 | 3,297 | Placebo; CVOT | January 2016 | Ongoing |

*-- by Emily Regier and Kelly Close*