MEMORANDUM

Novo Nordisk announces positive topline phase 3a results for semaglutide - July 13, 2015

Executive Highlights

- Novo Nordisk announced positive topline results late last week from the SUSTAIN 1 phase 3a trial of its once-weekly GLP-1 agonist semaglutide demonstrating superior ~1.5% A1c reductions vs. placebo.

Novo Nordisk announced positive topline results late last week from the SUSTAIN 1 phase 3a trial of its once-weekly GLP-1 agonist semaglutide. The randomized, double-blind trial (Clinical Trials.gov Identifier: NCT02054897; n=388 drug-naïve patients with type 2 diabetes) demonstrated that both 0.5 mg and 1.0 mg doses of semaglutide produced significantly greater A1c reductions (1.5% and 1.6%, respectively) vs. placebo (no A1c change; mean baseline A1c = 8.1%). In addition, significantly more patients achieved an A1c <7% with semaglutide (74% of the 0.5 mg group and 73% of the 1.0 mg group) than placebo (25%). Both doses of semaglutide also led to superior weight loss (3.8 kg with the 0.5 mg dose and 4.6 kg with the 1.0 mg dose) compared to placebo (1.0 kg; mean baseline = 92 kg). Semaglutide appeared to be safe and well tolerated; as expected, GI side effects (primarily nausea) were the most common adverse events and they were essentially on par/more/less than with the highly successful $2 billion/year drug once-daily Victoza. We believe a once-weekly version could grow the franchise meaningfully. The press release stated that these side effects were comparable to those seen in similar trials of Victoza (liraglutide) and that they diminished over time. Discontinuation rates for all adverse events were 6% and 5%, respectively, with the two semaglutide doses vs. 2% with placebo.

These results are certainly encouraging, if not particularly surprising and we believe this formulation could meaningfully expand Novo Nordisk's GLP-1 franchise as well as, of course, expand the market overall. SUSTAIN 1 is the first of six phase 3 trials for semaglutide (see the table below), and the press release indicated that topline results from the remaining studies (including the SUSTAIN 6 CVOT) are expected within the next nine months, consistent with guidance from Novo Nordisk's 1Q15 update. The remaining trials, several of which have active comparators, should offer a more complete picture of semaglutide's efficacy compared to other diabetes drug classes. They should also provide an indication of the product's usefulness at various places in the type 2 diabetes treatment algorithm; positive results from all of the trials would constitute a strong evidence base for semaglutide's versatility. Assuming no changes to this timeline, an FDA approval would likely arrive in late 2016. The introduction of semaglutide should certainly help Novo Nordisk compensate for any market share Victoza loses to Lilly's once-weekly GLP-1 agonist Trulicity (dulaglutide), which has performed extremely well since its launch - as long as it is easy to use - liraglutide certainly has this advantage and we think Lilly's Trulicity competes very well on this front, which should be market-expanding overall. Novo Nordisk also has several other intriguing programs for semaglutide on its agenda, including an oral formulation and a possible obesity indication - see below for more.

- **We look forward to learning more about Novo Nordisk's plans for semaglutide during its 2Q15 update on Thursday, August 6.** We also hope to hear updates on the status of Tresiba (insulin degludec) and Ryzodeg (insulin degludec/insulin aspart); the FDA accepted the Class II Resubmissions for the products in April, meaning a decision should arrive toward the end of the year. We assume an AdComm is unlikely since it would require unblinding interim data from the ongoing DEVOTE CVOT, but it is conceivable that the FDA could hold some sort of closed-door meeting with the firewalled team.

- **Novo Nordisk has confirmed that it will decide whether to advance an oral formulation of semaglutide into phase 3 trials in 2H15, though not before its 2Q15 update on August 6 (as had been speculated recently).** This is slightly earlier than the end-of-year deadline provided in the company's 4Q14 update, and we assume that the decision will likely be positive. Bioavailability appears to be the main challenge with oral GLP-1 agonists, as oral semaglutide required a 280x dose to match the efficacy of its injectable counterpart in phase 2 trials.
- **Novo Nordisk suggested in its 1Q15 update that phase 2 dose-ranging trials of injectable semaglutide for obesity could begin around the time of an approval in diabetes.** Management had previously indicated that these trials could potentially begin in 2015, but this latest statement suggests that late 2016 is a more accurate timeline. Brain scan findings have supported the possibility of greater weight loss with semaglutide compared to liraglutide, which would also place the drug ahead of all other existing obesity drugs in terms of efficacy. As was also touched upon in the 1Q15 call, we also imagine that Novo Nordisk will eventually shift some of its current research efforts for Victoza (e.g., in type 1 diabetes and NASH) over to semaglutide given that it has a longer patent life.

Table 1: SUSTAIN phase 3 trial program for semaglutide

Trial	Estimated Enrollment	Comparator/Design	Estimated Primary Completion Date
SUSTAIN 1	390	Placebo	May 2015
SUSTAIN 2	1,200	Merck's Januvia (sitagliptin)	October 2015
SUSTAIN 3	798	AZ's Bydureon (exenatide)	July 2015
SUSTAIN 4	1,047	Sanofi's Lantus (insulin glargine)	September 2015
SUSTAIN 5	397	Placebo; add-on to basal insulin and/or metformin	November 2015
SUSTAIN 6	3,297	Placebo; CVOT	January 2016

We note that there are not currently plans to test this against Sanofi's Toujeo - we think these results, as well as a trial vs. Novo Nordisk's own Tresiba, would be quite interesting. We are surprised there is not a trial vs. an SGLT-2 - we also think a trial using semaglutide with an SGLT-2 would be very interesting to see since there could be quite compelling results in terms of duration of effect.

-- by Emily Regier and Kelly Close