Closer Look

MEMORANDUM

Novo Nordisk receives positive CHMP opinion for Xultophy (IDegLira) - July 25, 2014

Executive Highlights

- The EMA's CHMP adopted a positive opinion on Novo Nordisk's GLP-1 agonist/basal insulin combination Xultophy (IDegLira; liraglutide/insulin degludec).
- A final EMA decision is likely within the next two to three months, with a launch expected in 1H15.
- A US filing for Xultophy is dependent on the re-submission of Tresiba, which is currently expected in late 2015.

Earlier today, Novo Nordisk announced that it received a positive opinion from the EMA's Committee for Medicinal Products for Human Use (CHMP) for Xultophy (also known as IDegLira), a fixed-ratio combination of the GLP-1 agonist Victoza (liraglutide) and the ultra-long-acting basal insulin Tresiba (insulin degludec). This means that a decision (likely an approval) should arrive within the next two to three months, which would represent a total review cycle of ~15-17 months (the therapy was first filed on May 31, 2013). The Novo Nordisk press release states that company expects to launch Xultophy (if approved) in 1H15. It is very exciting to see the GLP-1 agonist/basal insulin combination class so close to finally reaching patients, given the demonstrated strong efficacy and balanced safety profile (see below).

- **The proposed indication for Xultophy is:** "the treatment of adults with type 2 diabetes mellitus to improve glycaemic control in combination with oral glucose-lowering medicinal products when these alone or combined with basal insulin do not provide adequate glycaemic control." Interestingly, patients currently on oral drugs and a GLP-1 agonist do not appear to be explicitly included in this definition - we wonder if this will be a meaningful restriction, or if it will be easy enough for European providers to prescribe Xultophy off-label to this group.
    - **The specific indication is likely rooted in the data package that was submitted to the EMA, which only included the results from the DUAL I and II trials (see below).** DUAL I enrolled patients not at goal on oral drugs alone, while DUAL II enrolled patients who were already on basal insulin. DUAL III (which we saw first results for during Novo Nordisk's 1Q14 update) was the first to test Xultophy in patients uncontrolled on GLP-1 agonists - it is likely that this dataset could eventually support an expanded indication for Xultophy.
- **Although we would of course have preferred to see a US regulatory filing proceeding in parallel with the European filing, the 2013 FDA Complete Response Letter for Tresiba precluded that possibility** - Tresiba was approved in Europe around the same time. The initial FDA ruling was particularly surprising because the Advisory Committee convened to assess the candidate voted 8-to-4 in favor of approval. Our disappointment with the CRL was due in large part to the fact that it would push back the timeline for Xultophy in addition to Tresiba. As of the company's last update, the DEVOTE CVOT for Tresiba is expected to finish in mid-2015.
- **Management shared during Novo Nordisk's ADA Analyst Call that the company hopes to price IDegLira based on a sum-of-its-parts model** - this would still be a plus for patients due to the consolidation of copays. This would, however, mean that the product would be on the costly side, as Novo Nordisk is currently pricing Tresiba at a fairly high premium that has led (in some markets) to slightly slower uptake (see our Novo Nordisk 1Q14 report). Novo Nordisk

management has defended its pricing strategy: memorably, during the company's 3Q13 update, management made the frank point that Europe must share the burden of funding innovation along with the US. More recently, during a panel discussion at the Barbara Davis Center's 2014 Keystone Conference, Drs. Irl Hirsch (University of Washington, Seattle, WA) and Philip Home (Newcastle University, Newcastle upon Tyne, UK) discussed how the US market is bearing a disproportionate burden of funding innovation. The reimbursement environment in the EU is increasingly challenging, however, and it is an open question whether the majority of government and private payers will be willing to bear a high premium, even for a compelling product like Xultophy.

- **The DUAL phase 3 study program for IDegLira is one of the strongest data packages we have seen in the recent past for a diabetes therapy.** Dr. John Buse (University of North Carolina, Chapel Hill, NC) presented the results from DUAL I at ADA 2013 - Xultophy led to a mean 1.9% reduction in A1c compared to reductions of 1.4% with Tresiba and 1.3% with Victoza (mean baseline of 8.3%). Xultophy was also associated with a 32% reduction in hypoglycemia and less weight gain relative to Tresiba and less nausea than Victoza. DUAL II, presented at IDF, was a more complex trial design that was somewhat harder to interpret, but the efficacy seen there was also impressive (A1c reduction of 1.9% relative to 0.9% with Tresiba alone).
- **The other primary candidate in the GLP-1 agonist/basal insulin combination field is Sanofi's LixiLan, a fixed-ratio combination of the market-leading basal insulin Lantus (insulin glargine) and the relatively new short-acting GLP-1 agonist Lyxumia (lixisenatide).** As of the last updates from Sanofi and Zealand, LixiLan is on track for regulatory filing in late 2015. LixiLan's timeline was pushed back in the US as well, also due to regulatory difficulties. In Sanofi's case, it was the risk of interim data disclosure from the ELIXA CVOT for Lyxumia that prompted the company to withdraw its FDA NDA and instead wait until ELIXA finishes in 2015. The FDA will be holding a hearing on the topic of interim CVOT data disclosure in August, and we hope that stakeholders and the Agency can develop a new paradigm for drug approval that does not require completely unblinding an ongoing trial (which can damage or destroy the trial's integrity).
    - **At ADA, we got to see the first phase 3 data on LixiLan:** the results were impressive, but the comparison between LixiLan and Lantus monotherapy may have been affected by a very strong showing from the Lantus arm. Both arms achieved similar and striking A1c reductions (1.8% reduction on LixiLan compared to 1.6% on Lantus from 8% baseline) to a final A1c of 6.3% with LixiLan that was superior to the 6.5% achieved with Lantus, as LixiLan blunted postprandial glucose excursions substantially more than Lantus (LixiLan reduced excursions by 70 mg/dl compared to 12 mg/dl on Lantus; $p<0.001$). The strong efficacy seen in the Lantus arm may attest to investigators' skill with insulin titration - in the real world, it is hard to imagine that 1.6% mean A1c reductions from basal insulin monotherapy would be readily achievable.

CLOSE CONCERNS QUESTIONS

- How will payers in Europe assess Xultophy? Will they be willing to accept a sum-of-its-parts pricing model?
- Has Novo Nordisk's clinical trial program satisfied the narrow requirements of the German Federal Joint Committee (G-BA), which has recently forced the withdrawal of other diabetes drugs by stripping those drugs of their pricing premiums?
- What will the first European launch countries be for Xultophy?
- How soon following Tresiba's FDA re-submission might Novo Nordisk submit Xultophy in the US?
- What will the Xultophy device (and resultant patient experience) be like?
- To what extent will the indication for Xultophy (which at this point does not explicitly mention patients on a GLP-1 agonist) be a limit for certain patient groups, in terms of limits on either

prescribing or reimbursement? Could Novo Nordisk use more recently acquired data (for example, from DUAL III) to expand the indication? If so, how soon?

-- by Manu Venkat, Emily Regier, and Kelly Close