Closer Look

MEMORANDUM

Lilly provides new topline phase 3 results on novel basal insulin peglispro (BIL) in type 1 diabetes - September 7, 2014

Executive Highlights

- Topline results from two phase 3 trials for Lilly's novel basal insulin peglispro (BIL) in type 1 diabetes demonstrated superior A1c reductions vs. Sanofi's Lantus, along with weight and nocturnal hypoglycemia benefits.
- However, some of the same safety signals that emerged in previous phase 2/3 trials were also seen, including increases in triglycerides and liver enzymes.
- In addition to those signals, the press release mentioned that type 1 diabetes patients on BIL experienced significantly more total and daytime hypoglycemia, as well as modest increases in LDL and (in one of the trials) blood pressure.

On Thursday, Lilly announced topline phase 3 data on its novel basal insulin peglispro (BIL) from IMAGINE-1 and IMAGINE-3, two trials in type 1 diabetes patients. For background, topline results from three phase 3 IMAGINE trials in type 2 diabetes were announced in May, demonstrating superior A1c reductions compared to Sanofi's Lantus (insulin glargine) along with nocturnal hypoglycemia and weight benefits. The type 1 diabetes results were largely consistent with the results for type 2 diabetes, once again besting Lantus in terms of A1c, weight, and nocturnal hypoglycemia. However, in addition to the increase in liver enzyme levels and slightly worrying lipid changes seen in type 2 diabetes patients, the press release mentioned that there was an increase in total hypoglycemia (driven by daytime hypoglycemia) seen with BIL, as well as an increase in severe hypoglycemic events in IMAGINE-1. See below for a full overview of the topline type 1 diabetes results.

Additionally, the press release noted that IMAGINE-7 (which was testing flexible dosing of BIL, similar to what is possible with Novo Nordisk's Tresiba [insulin degludec]) found no significant difference between BIL dosed at the same time each day vs. variable dosing in type 1 diabetes patients - flexible dosing, if it makes it onto the product label, will help BIL stack up at least comparably with Tresiba from a patient convenience perspective. IMAGINE-6 found BIL superior with regards to A1c reduction relative to NPH in type 2 diabetes patients. In both trials, BIL's adverse effect profile was similar to what has been seen in other IMAGINE trials.

The timing of this announcement is consistent with previous guidance of 3Q14 for this topline data. With the completion of IMAGINE trials 1,3,6, and 7, Lilly has completed the set of core pivotal phase 3 trials for BIL. The company is on track for US and EU regulatory filings for BIL by the end of 1Q15. Overall, the topline type 1 diabetes results confirm that BIL is a relatively high-risk/high-reward candidate, with clear benefits (it has been quite difficult for new basal insulins to demonstrate A1c-lowering superiority against Lantus, but BIL has done it across its phase 3 program) but some quite worrying effects on liver enzymes and cardiovascular parameters such as lipids and (in one trial) blood pressure. This type of candidate, we imagine, would be able to benefit from some form of a conditional approval in a sub-population that could benefit from one or more elements of BIL's clinical profile; for example, patients at high risk for nocturnal hypoglycemia or with particular need for less weight gain.

Included below is a review of the topline results from IMAGINE-1 and IMAGINE-3:

- **Overview of trial design:** IMAGINE-1 was a 78-week open label study comparing BIL (n=295) with insulin glargine (n=160) in combination with mealtime insulin in type 1 diabetes patients.

IMAGINE-3 was a 52-week double-blind randomized study comparing BIL (n=664) with insulin glargine (n=450) in combination with mealtime insulin in type 1 diabetes patients.

- **Glucose-lowering efficacy:** At multiple time points (52 weeks for IMAGINE-3 and 26, 52, and 78 weeks for IMAGINE-1), BIL led to statistically significantly lower A1c levels compared to insulin glargine, and also helped significantly more patients achieve an A1c goal of under 7% than insulin glargine. Usually the use of the term "superiority" with regards to A1c reduction means that the difference surpassed a certain pre-specified superiority margin decided on by a trial's sponsors, but it was not specified what the margin was in this case. These results make BIL the first basal insulin to consistently demonstrate A1c-lowering superiority versus the market-leading Lantus, which is a huge accomplishment given that with each step forward in basal insulin therapy, there is less and less room for improvement.
- **Non-glycemic efficacy:** Making the efficacy results even more impressive, in both trials, patients experienced weight loss (notably, better than less weight gain) when treated with BIL despite a greater A1c reduction. This is a slight difference from the phase 3 results in type 2 diabetes, in which patients on BIL experienced less weight gain rather than weight loss.
- **Hypoglycemia:** Hypoglycemia appears to be one of the biggest points of differentiation between BIL and insulin glargine, although not exclusively in a positive way, as we learned with this most recent set of topline results. Keeping with the results in type 2 diabetes, in IMAGINE-1 and IMAGINE-3 BIL led to significantly less nocturnal hypoglycemia than insulin glargine. However, worryingly, the studies found a statistically significant increase in total hypoglycemia, driven by an increase in daytime hypoglycemia. In IMAGINE-1, patients also reported a significantly greater rate of severe hypoglycemia, while in IMAGINE-3 there was a non-significant trend towards fewer severe events with BIL - a low overall number of severe events could possibly explain the divergent results.
    - **We have to hand it to Professor Philip Home (Newcastle University, Newcastle upon Tyne, UK), who nearly perfectly predicted the split effect on daytime and nocturnal hypoglycemia with hepato-selective insulin during a presentation at CODHy Latin America earlier this year -** that talk is a must-read for those interested in BIL and liver-selective insulins in general. Dr. Home specifically suggested that hepato-specific insulin would likely have a benefit during the night, but more hypo during the day. In the daytime, hepatic glucose production guards against hypoglycemia during times of increased energy consumption. Hepato-specific insulin would have a particularly strong inhibitory effect on hepatic glucose production, which could increase patients' risk of daytime hypoglycemia. At rest, however, hypoglycemia is due more to insulin-stimulated glucose uptake in the periphery, which would be less of a factor with a hepato-specific insulin, causing a drop in nocturnal hypoglycemia.
- **Other safety concerns:** The safety signals seen in some or all of the phase 3 trials in type 2 diabetes were seen in the type 1 diabetes studies as well: these included increases in liver enzyme ALT beyond three times the upper limit of the normal range, elevations in triglycerides and LDL, and reductions in HDL. With regards to liver safety, BIL led to increases in liver fat in a subset of patient studied with MRI, but there were no cases of severe liver injury (Hy's Law) in IMAGINE-1 or IMAGINE-3. In addition to the common safety signals between the type 1 and type 2 diabetes data, IMAGINE-3 found a modest but statistically significant increase in both systolic and diastolic blood pressure (<2mmHg).
    - **An analysis of all clinical trials in type 1 and type 2 diabetes found that the rate of major adverse cardiovascular events in patients taking BIL were similar, with a hazard ratio below 1 and the upper bound of the 95% confidence interval below 1.4.** However, given that the FDA's threshold for requiring post-approval outcomes study is 1.3, it remains an open question whether the agency would ask for a CVOT (which it very well might, given its conservative approach towards insulin as

evidenced by its Tresiba CRL). However, as we understand it, Lilly currently does not have plans to conduct a CVOT for BIL.

- **BIL is such a unique candidate in large part because of its liver-selective mechanism of action.** Although no phase 3 data on BIL was ready in time to present at ADA, Lilly did present the results of a mechanistic clinical study on BIL that confirmed its liver-selectivity.

-- by Manu Venkat and Kelly Close