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Safety concerns mean Lilly's novel Lantus competitor has much to prove

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Better than Lantus, but with more risk. That is the best that can be said for the novel basal insulin project for which Lilly has just reported the first phase III data. The peglylated version of the mealtime product Humalog showed superiority to Sanofi's mainstay long-acting insulin, but with safety signals that could make its approval pathway one that goes directly uphill.

With a panoply of insulins available, including two marketed long-acting products in the US, regulators are likely to take a long look at the liver enzyme elevations that emerged in Lilly's pivotal Imagine programme. The lesson of Novo Nordisk's Tresiba is instructive here, as cardiovascular signals have waylaid that project in the world's biggest drug market; Boehringer Ingelheim's decision to walk away from its partnership with Lilly on this project is proving to be wise (*Lilly diabetes risk-sharing starts to unwind as Boehringer pulls back, January 8, 2013*).

Superior, but...

It is impressive that the project, called basal insulin peglispro and codenamed LY2605541, managed to score superiority on blood-sugar control to Lantus, given that neither Novo's Levemir nor Tresiba have achieved this rather high standard. This could have made it a properly differentiated product, an important competitive quality given that Lantus is approaching its patent expiry in less than a year.

Therefore it was unfortunate for the Indianapolis-based group that data from the Imagine-2, 4 and 5 trials turned up worrying side-effects. Most important of these is the greater rate of increase in alanine aminotransferase to the important threshold of more than three times the upper limit of normal seen in patients taking the Lilly product compared with those on Lantus. In Imagine-5, patients who switched from another long-acting insulin also registered an increase in liver fat as measured by magnetic resonance imaging compared with those taking Lantus; that difference stabilised after 26 weeks.

The change in liver fat is also reflected in changes in blood lipid levels, although the data here are mixed. Patients in all three trials had small but statistically significant increases in triglycerides; in Imagine-4, in patients taking basal and mealtime insulin, and Imagine-5, patients taking the Lilly project saw a statistically significant decrease in the "good" high-density lipoprotein cholesterol compared with those taking Lantus. In Imagine-5, "bad" low-density lipoprotein declined compared with Lantus.

Lilly noted that researchers had measured no difference in adverse cardiovascular events between patients taking pegylated Humalog and those taking Lantus in all of the trials done to date. Nonetheless, the existence of a cardiovascular signal, no matter if mixed and challenged by the outcomes data, ought to be reason for concern; Tresiba was knocked out in the US by a statistically non-significant cardiovascular outcomes signal (*Dizzy day for Novo as FDA rejects Tresiba, February 11, 2013*).

Lilly said it would submit LY2605541 to the FDA and European regulators by the end of the first quarter in 2015.

Doubts

Analysts were unimpressed with the data. UBS's Marc Goodman acknowledged that the superiority finding helped LY2605541 competitively against Lantus, but cited safety concerns. "Current insulin is pretty good already," he wrote. "We would expect an interesting FDA panel engagement."

He did not alter his risk-adjusted forecast of $1bn in sales in 2020. *EvaluatePharma's* consensus reaches a lower figure: $636m.

Morgan Stanley analyst Amy Walker, who covers Sanofi, wrote, "We do not anticipate consensus revisions for Sanofi and remain confident in sustainability of its leadership."

Lantus loses patent protection next year and its sales are forecast to stabilise at about $10bn in 2016, slightly higher than the $7.6bn recorded last year. An additional $393m is expected from a new formulation called

U300 that aims to reduce the frequency of hypoglycaemia episodes.

Significantly, Lilly did not test against U300, so it is not clear how its long-acting insulin will perform against the lifecycle extension. However, given that Lantus is expected to dominate the space, the comparison might be unnecessary.

Expectations have remained much higher for Lilly's other chess piece, the biosimilar Lantus codenamed LY2963016. Tellingly, Boehringer has decided to remain Lilly's partner on this project, along with the non-insulin diabetic medications Tradjenta and Jardiance.

Given that the biosimilar looks to be more of a sure thing than the novel insulin, Lilly might want to put more emphasis on the former.

Trial	Population	ID
Imagine-2	Insulin naïve	NCT01435616
Imagine-4	Basal insulin with mealtime insulin	NCT01468987
Imagine-5	Basal insulin experienced	NCT01582451

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