Amylin's \$1 billion heavyweight deal

In November, Amylin announced a \$1 billion partnership with Osaka, Japan-based Takeda to codevelop and commercialize obesity treatments. Takeda paid the San Diego-based biotech \$75 million upfront for Symlin/metreleptin combination as part of an agreement that could exceed \$1 billion if certain development and sales-dependent milestones are hit. The deal also includes Amylin's amylinomimetic compound daivalintide, which is currently only in phase 2 studies. But, as Stephen O'Rahilly, director of the Metabolic Research Laboratories at the University of Cambridge in the UK, points out, Symlin (pramlintide) is already approved and is "used by a lot of type 1 diabetes patients to smooth out control and prevent the weight gain that happens when on insulin."

The agreement comes amid a surge of deals in metabolic disease, particularly for diabetes treatments that have potential weight loss benefits for the obese. For example, on December 23, Paris-based Sanofi-Aventis paid €100 (\$143) million for a 19.9% stake in Zealand Pharma. This Copenhagen-based biotech is developing a peptide analog of Amylin's Byetta (glucagon-like peptide 1 (GLP-1)/exendin 4) for type 2 diabetes, which has also shown efficacy in promoting weight loss. In what has become a crowded market, products will likely gain a competitive edge if they can fight both metabolic disease and obesity, the latter with a potential market of 300 million people worldwide.

Amylin already looks to have consolidated its position. According to Collins Stewart analyst Salveen Kochner, "They may not be first to market, but I think Amylin signed a nice partnership, so they're well-positioned if any of their drugs work."

The nearest competitor, she says, is Vivus, the Mountain View, California-based company, whose once daily capsule Qnexa (phentermine and topiramate) for the diabetes market achieved 15% weight loss in phase 3 trials. Elsewhere, Novo Nordisk has launched a long-acting GLP-1 analog Victoza (liraglutide; *Nat. Biotechnol.* **27**, 682–685, 2009) in Europe as a type 2 diabetes treatment. At present, the Copenhagen-based biotech still awaits a decision from the US Food and Drug Administration. Recent studies show Victoza to be more effective in helping people shed weight than the anti-obesity pill orlistat, marketed as Xenical by Roche and Alli by London-based GlaxoSmithKline.

But Amylin's foothold in the marketplace is further strengthened by its two first-in-class synthetic gut hormone drugs approved for type 2 diabetes—the insulin boosting glucagon-like peptide 1 (GLP-1) analog Byetta (exenatide), and Symlin. Symlin is a synthetic version of amylin, a neuroendocrine hormone secreted by pancreatic beta cells, that boosts insulin action and helps regulate appetite, food intake and glucose control. In diabetes sufferers, sensitivity to Symlin is often reduced over time, in much the same way that insulin sensitivity is lost. By combining Symlin with metreleptin, a recombinant version of human leptin (a hormone secreted by fat cells that acts on the hypothalamus to regulate food intake), the company hopes to treat obesity. Thus far, the drug combo has shown impressive weight loss in animal and human trials, and Amylin is expecting to announce favorable results from phase 2 trials following positive top-line data. The other drug included in the Takeda deal is daivalintide, a second-generation amylin receptor agonist, which mimics the action of amylin.

The path to approval for Amylin and its competitors won't be easy. Safety issues that led to the withdrawals of the cannabinoid receptor antagonist Acomplia (rimonabant) and, before that, appetite suppressant Redux (dexfenfluramine), mean that novel products are likely to face intense scrutiny. In a recent study, the Symlin/metreleptin combination produced impressive weight loss in a broad population of obese people, but a subanalysis showed less dramatic effects in severely obese individuals. And, according to Tom Hughes, CEO of obesity therapeutics company Zafgen, headquartered in Cambridge, Massachusetts, although Amylin's injectable is more expensive and inconvenient than an oral drug, the 'hormone replacement' approach avoids the idiosyncratic toxicity inherent to small molecules. "I think that may be at the heart of why this deal got as much as it did at the stage that it's at," he says. "It is appealing on a number of levels to think that you're giving back something that is important or missing, which is restoring the balance to the patient and leading to the effect." However, John Wilding, a clinical researcher at the University of Liverpool, UK, says there's only a nugget of truth in the claim. Pharmacological doses are orders of magnitude higher than physiological concentrations, and in type 2 diabetes, amylin levels actually tend to be high.

Hayley Birch

Amylin has gained a strong position in the already crowded metabolic disease marketplace.

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