Sanofi drops MannKind's inhaled insulin

Nearly a year after launching Afrezza, a fast-acting inhaled form of powdered human insulin, Paris-based Sanofi is returning rights to the drug to its developer, MannKind. The January 5 announcement triggered an almost 50% drop in the Valencia, California, biotech's stock price, leaving the company bloodied but, at least for the short term, unbowed.

Afrezza, MannKind's only product, was approved by the US Food and Drug Administration (FDA) in June 2014. The company positioned the inhalable insulin as an option for people with type 1 and type 2 diabetes to use at mealtimes. When Sanofi launched Afrezza in February 2015 this market was estimated at $25.8 million in the US.

But sales efforts gained little traction. Despite preparing for launch for eight months, Sanofi recorded a meager €7 million ($7.7 million) in revenue for 2015. The large pharma had licensed worldwide rights to Afrezza from MannKind in August 2014, paying $150 million upfront and promising up to $775 million in milestones. The latter number included up to $650 million upon achievement of certain sales thresholds, none of which were met.

This is not the first time inhaled insulin has failed to find a following. Sanofi, a long-time leader in diabetes care, developed the first such product, Exubera, with New York–based Pfizer, and sold its share of rights to the drug to Pfizer in 2006, weeks before it was approved by the FDA. Roughly one year later, after disappointing sales (just $9 million in the first nine months of 2007), Pfizer withdrew the product from the market (*Nat. Biotechnol.* **25**, 1331, 2007).

Soon after acquiring rights to Afrezza, Sanofi's then-CEO Christopher Viebacher emphasized differences between it and Exubera. He mentioned the device's ease of use, and the drug's pharmacokinetic profile—a quick on-and-off response that better mimicked natural insulin responses to food intake. Afrezza could also facilitate individuals' transition from oral therapies to injectable diabetes products, he said, a move which many patients are reluctant to make.

Those differences did not convert to success. But MannKind believes a change in marketing and sales strategies can make a difference.

"Afrezza is definitely here to stay," new CEO Matthew Pfeffer told the audience at the JP Morgan Investor Conference in San Francisco on January 13. Pfeffer called it a "fundamentally different product with some significant advantages if used the right way."

MannKind will abandon Sanofi's premium pricing strategy to improve prospects for reimbursement from insurers, said Pfeffer. He also emphasized the company's intention to use social media to inform patients and caregivers about the benefits of Afrezza, and to roll out education programs to lower the user dropout rate. "We started hearing more and more that…people were not getting the results that they thought they were going to get," he said, largely because of inexperience in titrating to the optimal dose or "not hanging in there" to see the benefits.

Despite these measures, lingering questions that have dogged the product, including suspicions of increased risk of lung cancer, are unlikely to be assuaged. Experts at the FDA Advisory Committee in April 2014 acknowledged available data were insufficient to provide clear answers. "The data and the background science create concern," acting chairperson Robert Smith of the Alpert School of Medicine of Brown University in Providence, Rhode Island, said at the time—especially given that exposing cells within the lung to doses of insulin would likely activate insulin-like growth factor receptors, a pathway known to be involved in tumor cell proliferation.

MannKind

Small enough—what's the issue then?

The company is also keen to open other commercial opportunities for its inhalation technology. The insulin in Afrezza was formulated using the company's microparticle technology. This consists of inducing the small-molecule excipient fumaryl diketopiperazine to assemble into particles onto which drug molecules can be loaded. MannKind is testing inhaled forms of the vasodilator treprostinil for pulmonary arterial hypertension; palosetron, a 5-HT3 antagonist for chemotherapy-induced nausea; and the adrenalin epinephrine for anaphylaxis.

On January 21, MannKind also announced an agreement with newly formed Receptor Life Sciences in Seattle, to explore the potential to develop inhaled formulations of compounds to treat conditions such as chronic pain, neurologic diseases and inflammatory disorders. MannKind will transfer manufacturing technology and will be eligible to receive development and commercialization milestones of up to $102.25 million as well as royalties on product sales. Receptor will be responsible for all development costs. Little has been disclosed about Receptor except that MannKind's former vice president, pharmaceutical research and development, Andrea Leone-Bay, joined the company last fall as CSO.

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