Cystic fibrosis drug Vertex's latest triumph

Cambridge, Massachusetts–based Vertex Pharmaceutics has won approval to start selling Kalydeco (ivacaftor) for a rare form of cystic fibrosis. The US Food and Drug Administration's nod on January 31 was lightning fast—only three months after Vertex filed the application—yet it represents a step that patients have been anticipating for over 20 years. Kalydeco builds directly upon the 1989 discovery that the disease is caused by mutations in the cystic fibrosis transmembrane conductance regulator gene (*CFTR*). Only a small percentage (4%) of patients, however, have the G511D mutation in *CFTR* against which Kalydeco acts. Thus, Vertex has plans to explore the drug's potential in cystic fibrosis patients with other mutations and to further penetrate the market.

Kalydeco is the first disease-modifying therapy approved for cystic fibrosis. The disease is caused by mutations in the *CFTR* gene that encodes a chloride-selective ATP-binding cassette transporter. Defects in this ion transporter affect the transport of chloride and other ions across the cell membrane, leading to problems in the secretion of digestive enzymes and mucus. A wide variety of *CFTR* mutations can interrupt this activity, leading to poor weight gain due to pancreatic insufficiency, diabetes, and the build-up of thick, sticky mucus that can clog airways in the lung and promote infection.

Over the years, attempts to correct the defect with experimental gene therapy or small-molecule modulators failed, and clinicians were confined to managing symptoms. The median life expectancy for those with cystic fibrosis has grown dramatically in recent years but still hovers around 37. And people with cystic fibrosis typically spend hours a day on healthcare, taking as many as a dozen medications and high-calorie supplements, and wearing therapy vests that thump their chests to loosen the mucus in their lungs, says Bonnie Ramsey, a pediatric pulmonologist at Seattle Children's Hospital in Washington. "We don't know yet whether these other therapies will decrease once a patient starts taking Kalydeco," she says. "But at least they're not being hospitalized and getting i.v. antibiotics as often."

Boston Globe via Getty Images

Vertex now has a novel CF drug on its hands after the FDA approved Kalydeco.

Kalydeco appears to open G511D mutant channels, which otherwise fail to gate properly. In phase 3 trials, Kalydeco boosted lung function by 10% in 161 patients taking the drug compared with those on placebo, measured by forced expiratory volume in one second (FEV1) as well as improvements in weight gain and reduced cough and sputum production. Only 1,200 people in the US have the G511D mutation, and the drug—which is priced at $294,000 a year—is approved only for those over the age of six. But by the middle of this year, Vertex aims to launch a series of clinical trials to expand that label. A pediatric study will evaluate the drug in patients between two and five years old, another trial will seek to expand use of the drug in other CFTR gating mutations and a third will specifically target a class of mutations called R117H, which also affects gating but retains some degree of chloride ion transport. Expansion into these patient populations could roughly double Kalydeco's market.

The Kalydeco approval marked the second success in less than a year for Vertex, which includes Incivek (telaprevir), a landmark hepatitis C drug that was approved last May. The sequential successes are a testament to the company's drug discovery and development platform, says Alan Carr, an analyst at the investment bank Needham and Company, based in New York. "A major challenge for a lot of midcap biotech companies is to get a second hit," he says. "It's impressive that Vertex has done that so quickly."

Yet it almost didn't happen. Vertex picked up its cystic fibrosis program when it bought a San Diego–based biotech company called Aurora Biosciences in 2001. At that time, getting drug companies to work on cystic fibrosis was a tough sell, recalls Robert Beall, chief executive of the Cystic Fibrosis Foundation (CFF) in Bethesda, Maryland. Beall launched the cystic fibrosis program at Aurora in 1998 when, frustrated with the slow pace of screening in academic laboratories, he called seven

IN brief

Diabetes once-weekly drug

After a third round through the US Food and Drug Administration, Amylin's Bydureon (exenatide) type 2 diabetes drug finally hit the US market in February. Bydureon was once anticipated to be a blockbuster drug but safety concerns delayed its approval (*Nat. Biotechnol.* **28**, 1224, 2010) and gave rival Victoza a head start. Bydureon was developed by the San Diego–based Amylin and Eli Lilly of Indianapolis as a long-acting formulation of its own drug Byetta (exenatide), an analog of the insulin-boosting glucagon-like peptide 1 (GLP-1), a first-in-class synthetic gut hormone. Although both contain the same active compound, Bydureon requires once weekly injections compared with Byetta's twice daily. Competitor Victoza (liraglutide) from Novo Nordisk in Princeton, New Jersey, also a GLP-1 agonist, was approved in early 2010 as a once-a-day injection. Victoza took 16 months to gain 50% of the share of prescriptions in its class, says Steve Yoo, a biotech analyst at Leerink Swann in New York. "That's a phenomenal market launch." Bydureon is unlikely to capture as much of the market as quickly, despite its less frequent dosing scheme, he adds. Acting against Amylin's new drug are the results of one trial, which showed Victoza was slightly better at controlling blood sugar than Byetta (*Lancet*, **374**, 39–47, 2009). Victoza is also less cumbersome for individuals to prepare and the needle is smaller than that for Bydureon. Nevertheless, Bydureon could still capture a big chunk of the market. There is a niche for once-weekly GLP-1, Yoo says, and priced at about $4,200 a year, "it's competitive to Victoza. We think the class will simply grow." As part of Bydureon's approval, Amylin agreed to several postmarketing requirements that include assessing thyroid cancer and pancreatitis risks, cardiovascular events and other health problems. *Gunjan Sinha*

IN their words

"They could care less. This shows they have no scruples. You know, you can't grow a conscience. And if they had one, they would have disassociated themselves from her as quickly as possible." David Kliff, publisher of *Diabetic Investor*, on Novo Nordisk's signing of TV chef and good old girl Paula Deen as a spokesperson after her disclosing that she has diabetes. (*Pharmalot*, 20 January 2012)

"The fact that I ended up where I ended up, you have to believe [my] prayers were answered." Joe Beery, who works at Carlsbad, California–based Life Technologies. Beery's twins were suffering from a misdiagnosed and mistreated condition for a decade, until Beery took a job at Life Technologies. Genome researchers at Baylor in Houston with support from Life Technologies, correctly diagnosed and successfully treated the Beery twins. (*Bloomberg Business Week*, 30 January 2012)