Sanofi to propel inhalable insulin Afrezza into market

MannKind has found a deep-pocketed business partner to market its inhaled insulin therapy, Afrezza (Technosphere insulin). On August 11, Sanofi agreed to pay $150 million upfront and $775 million in sales and development milestones. The US Food and Drug Administration (FDA) approved Afrezza in late June as a prandial insulin to improve glycemic control in individuals with either type 1 or type 2 diabetes (T1D and T2D). For the Valencia, California–based biotech, it was 'third time lucky' with the FDA—finally gaining approval for its powdered insulin, which is administered by inhalation rather than injection. Afrezza is also the last inhaled insulin standing—the other three fell by the wayside: Pfizer's Exubera, after a disastrous commercialization, and Aradigm/Novo Nordisk's insulin Diabetes Management System (iDMS) and Alkermes/Eli Lilly's AIR insulin both during development. MannKind and its billionaire founder, Alfred E. Mann, have also had their fair share of regulatory setbacks—getting the product to market has eaten up >$2.3 billion in funding (*Nat. Biotechnol.* **29**, 175–176, 2011). And though the approval is a coup for a product that many investors had long written off as too risky, the Paris-based pharma's modest upfront payment indicates a cautious attitude to Afrezza's potential market share.

Afrezza is a short-acting insulin therapy for people with diabetes who require mealtime insulin. It comprises recombinant insulin particles, manufactured by Amphastar Pharmaceuticals, of Rancho Cucamonga, California, absorbed into 'Technosphere' particles formed with the excipient carrier, fumaryl diketopiperazine powder (FDKP). FDKP self-assembles through hydrogen bonding in a mildly acidic environment to form microspheres. The dry powder is delivered by a thumb-sized inhaler system, the DreamBoat (Gen2) device. It is not a substitute for long-acting insulin and, in patients with T1D, must be used in combination with long-acting insulin, such as Sanofi's Lantus or Novo Nordisk's Levemir, which lasts a full day. Patients might find a puff of insulin at the beginning of a meal preferable to an injection. But diabetics and caregivers will need to weigh the inhaled drug's convenience over its potential long-term safety issues for the lungs.

FDA approved Afrezza with a risk evaluation and mitigation strategy, requiring four postmarketing trials—a pediatric trial, a five-year trial to assess lung cancer risk in 8,000 to 10,000 patients and two pharmacokinetic/pharmacodynamic trials. In addition Afrezza will have a boxed warning, and prospective patients will have to undergo lung function tests to receive a prescription. All of these factors cast doubt on whether clinicians and patients will be willing to opt for Afrezza.

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Small enough for a dinner party: MannKind's insulin inhaler.

Clinching a deal with Sanofi is certainly helping this novel drug-device combination get started. "It's very important for the launch to be strong out of the gate," says Christopher James, managing director and senior biotech analyst at New York–based Brinson Patrick Securities, on the need for a marketing partner. An earlier inhaled insulin, Pfizer's Exubera, which was withdrawn from the market after disappointing sales, may cast a pall on the newcomer's prospects (*Nat. Biotechnol.* **25**, 1331–1332, 2007). Arlinda Lee, senior healthcare analyst at the New York–headquartered investment bank MLV, which brokered a secondary stock offering for MannKind, is optimistic about the drug's launch but underlines the prevailing attitude of caution. "People in general think that an inhalable insulin isn't really viable," Lee says.

Afrezza's improved features compared with previous inhaled insulins could eliminate some barriers to adoption. For example, the Exubera device aerosolized insulin within a chamber that was so large and unwieldy some compared it to a bong. Aradigm's iDMS inhaler was also a heavy and bulky battery-operated electronic device that required refrigeration. In contrast, Afrezza's delivery device, the Dreamboat inhaler, is far smaller, roughly the size of a thumb. Another plus is Afrezza's pharmacokinetic profile that closely mimics the activity of endogenous insulin. After inhalation, the Technosphere insulin powder dissolves in the lungs, leaving the insulin to enter arterial circulation directly. Using Afrezza, insulin in circulation peaks in

CAR-T cell therapy gets breakthrough status

In July, the first chimeric antigen receptor T (CAR-T) cell–based immunotherapy received breakthrough drug designation from the US Food and Drug Administration. The University of Pennsylvania's CTL019, developed in partnership with Novartis, received the designation for its program in relapsed and refractive acute lymphoblastic leukemia (ALL). Early-stage clinical trial results of 27 ALL patients (22 children and 5 adults) reported last December at the annual meeting of the American Society of Hematology showed that 89% of patients had a complete response, although five relapsed, apparently due to non-CD19-bearing tumors. Competition in the field has been heating up. Kite Pharma of Santa Monica, California, and Juno Therapeutics of Seattle have CAR-T cell clinical programs. Preclinical CAR-T cell programs have been launched by Paris-based Cellectis and bluebird bio of Cambridge, Massachusetts, in partnership with Pfizer of New York and Summit, New Jersey–based Celgene, respectively.

NCATs drug candidate attracts first buyer

A drug candidate developed at the US National Institutes of Health (NIH)'s National Center for Advancing Translational Sciences (NCATS) and its collaborators to treat sickle cell disease has been acquired by Baxter International's bioscience unit. Baxter recently acquired AesRx of Newton, Massachusetts, an NIH collaborator in the Therapeutics for Rare and Neglected Diseases program, whose drug candidate, Aes-103, is the first specifically developed to target the underlying molecular mechanism of sickle cell disease. Baxter will advance the clinical development activities required for regulatory approval and commercialization.

"Starting from zero and going to 60 is not so easy, but once you're at 60 you can keep going at that rate." Kevin J. Whaley, CEO of Mapp Biopharmaceuticals of San Diego, the private biotech that developed the Ebola monoclonal antibody given to the two American healthcare workers infected with the virus in Africa. (*The New York Times*, 6 August 2014)

"If you ask us to figure it out for you, we will. But you may not like what we figure out." House Energy & Commerce vice chairman of the Health Subcommittee Michael Burgess (R-TX) suggests that insurance companies and drug makers should work together on payment mechanisms or risk government intervention at the July 11 American Enterprise Institute forum on Paying the Costs for Cures. (*RPM Report*, 15 July 2014)