Vertex CF triple drug roars to approval

Vertex Pharmaceuticals has won the US Food and Drug Administration's approval to start selling its triple-combination treatment Trikafta for cystic fibrosis (CF), extending the reach of the company's CF drugs to 90% of patients with the disease.

CF is a life-shortening multi-system genetic disease, caused by a defective version of the CFTR chloride channel that leads to problems in the lungs, pancreas, gastrointestinal tract, sweat glands and other organs. Common mutations that cause CF include Phe508del, carried by around 90% of patients in the United States, and give rise to CFTR proteins that are misfolded, that can get trapped in the endoplasmic reticulum, and that are not fully functional when they do traffic to the cell surface. Vertex has long been working on therapeutics to correct the shape of the protein to allow it to better traffic to the cell surface ('correctors') and to activate its function by holding it open at the cell surface ('potentiators'). Trikafta combines ivacaftor, tezacaftor and elexacaftor. Ivacaftor was first approved as the monotherapy Kalydeco by the FDA in 2012 and is a 'potentiator' that helps keep mutated CFTR in an open state. At that time, however, it was only approved for around 5% of cystic fibrosis patients. Tezacaftor is a 'corrector', approved in 2018 in a combination with ivacaftor sold as Symdeko. By combining ivacaftor and tezacaftor with another 'corrector', elexacaftor, the company has improved the reach and efficacy of its cystic fibrosis drugs.

Elexacaftor, the newest corrector and a key component of Trikafta, went from first synthesis to combination approval in the record-breaking time of under four years, says Reshma Kewalramani, chief medical officer at Vertex and incoming CEO. "It really does sound unbelievable, but it is true," she adds.

Vertex anticipates $3.7 billion in sales from its CF portfolio in 2019. The $300,000-plus annual price tag for these drugs frequently draws fire, however. The Cystic Fibrosis Foundation, which backed and profited from the discovery and development of Vertex's CF candidates, has set up a research agenda to find drugs for the 10% of patients who don't benefit from available options, which includes work on mRNA-based drugs, gene replacement therapies and gene editing treatments.

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than with the antibodies," he says. But no such reduction was observed. "They're all pure LDL-lowering drugs," he says.

They work by preventing extracellular PCSK9 from forming a complex with LDL receptors expressed by hepatocytes, which otherwise would lead to lysosomal degradation of the PCSK9-bound receptors. Instead, after internalizing LDL-C, the receptors enter a recycling pathway, through which they return to the hepatocyte surface and participate in another cycle of LDL-C removal. The antibody drugs, which lower LDL-C by approximately 60%, appear to be slightly more potent than inclisiran, which in clinical trials lowers LDL-C by approximately 50%. But that difference will not translate into a large difference in absolute terms, Kastelein thinks, particularly because the rollout planned for inclisiran, which involves twice-yearly dosing at a doctor's office, may help to ensure high patient adherence. After inclisiran reaches the market, Kastelein is anxious to avoid a replay of the 'statin wars' of recent decades, when rival products were promoted on the basis of minimal differences in pharmacological activity. "I found that to be totally irrelevant at the time," he says.

To be considered competitive, inclisiran will need to demonstrate a significant decrease in the risk of major cardiovascular events such as heart attack or stroke; to reduce the need for revascularization procedures, such as bypass surgery or angioplasty and stenting; and potentially to reduce the risk of death. Although the cardiovascular-outcome trials of Repatha and Praluent are not directly comparable because of differences in the patient populations recruited into each study and in the length of follow-up involved, Repatha reduced the risk of heart attack by 27%, the risk of stroke by 21% and the need for revascularization by 22%, whereas Praluent demonstrated a 15% reduction in mortality as well as a 15% reduction in the risk of major adverse cardiovascular events. The ORION-4 outcomes trial in 15,000 patients, according to Wijngaard, is designed to demonstrate reductions of 25% or greater in major adverse cardiovascular events and in death from cardiovascular events. The trial will also need to exhibit a comparable safety profile. As of October 2019, says Wijngaard, 382 patients in an open-label extension study, ORION-3, have received as many as eight doses of inclisiran over four years and have shown no reported liver toxicity effects.

Nabil Seidah, of the non-profit Montréal Clinical Research Institute, affiliated with the University of Montréal, cautions that inclisiran may not be appropriate for patients with liver damage, because PCSK9 seems to be involved in liver-tissue regeneration. "We have shown this at least in mice," says Seidah, who is one of the pioneers of PCSK9 research. "Removal of PCSK9 could have consequences in a situation where you need renewal." Inclisiran's twice-yearly dosing regimen could increase the potential risk, because therapy cannot be withdrawn in a timely fashion should a problem emerge. No such issues have become apparent in the four years that the two mAb-based PCSK9 inhibitors have been available. However, Seidah is, for the same reason, even more opposed to genome-editing-based approaches that would provide liver-specific knockdown of *PCSK9* expression. "If you remove the gene completely, that's it — there is no way back," Seidah says. "I think we're tinkering with genes where we don't know their functions so well."

One company that has nevertheless set out to achieve such an outcome is Verve Therapeutics. Verve aims to harness genome editing to confer lifelong protection against coronary artery disease. Its starting position is based on the past 15 years of research, which has uncovered individuals carrying mutations in various genes involved in lipid and lipoprotein metabolism who have a substantially lower risk of cardiovascular disease than the general population. Verve has not yet publicly unveiled its list of candidate-gene targets, but its general approach is based on recapitulating the protective effects of these loss-of-function mutations in a 'one-and-done' therapy. "Right now, we're in the process of developing a lead candidate," says Kathiresan. "We hope to be in the clinic in roughly three years." The company will start with individuals who have high genetic risk and established cardiovascular disease and thereafter pursue a stepwise approach to clinical development. Its target genes are involved in one of three pathways: LDL-C, which controls cholesterol; lipolysis, which breaks down dietary triglycerides; and lipoprotein(a), high concentrations of which are now considered to cause cardiovascular disease.

Among the list of potential candidates, *PCSK9* is the most heavily validated, because existing pharmacological and genetic evidence supports the safe elimination of its expression in the liver. Targeting *PCSK9* is also the most competitive space. Other potential targets include *ANGPTL3*, which encodes angiopoietin-like 3 protein, an endogenous inhibitor of lipoprotein lipase, an enzyme that is a key regulator of triglycerides, cholesterol, glucose and energy metabolism in the liver.

Also targeting *ANGPTL3* mRNA is an antisense oligonucleotide therapy from Ionis and its affiliate Akcea Therapeutics, which is currently in phase 2 studies. Meanwhile, other developers continue to target