WSJ: Startup Aims to Revive Failed Drug

DalCor is mounting 5,000-patient trial of cholesterol drug that Roche shelved after phase 3 failure.

A study led by Jean-Claude Tardif, director of research at the Montreal Heart Institute, identified a genetic variation linked to a benefit for dalcetrapib. The drug failed to show an overall benefit in a study of nearly 16,000 patients. PHOTO: MONTREAL HEART INSTITUTE

By RON WINSLOW

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A London-based startup is making a risky bet that a surprising genetic variation will enable it to find success in one of the pharmaceutical industry's biggest flops.DalCor Pharmaceuticals said it has raised $150 million in venture financing to mount a 5,000-patient trial of a cholesterol drug called dalcetrapib that Roche Holding AG shelved after the pill failed to prevent heart attacks and strokes in a phase 3, or late-stage, study of nearly 16,000 patients.

DalCor's plan is based on a DNA analysis of patients in the Roche study that revealed a variation in a single gene was associated with a 39% reduction in heart attacks and strokes. About 20% of patients had the favorable variant. A corresponding variant in the same gene was linked to a heightened risk.

The company will enroll only patients with the favorable genetic signature in its study, hoping to rescue the drug from the scrap heap.

The trial raises the provocative possibility that other failed drugs might be revived based on genetic variations that affect how patients respond.

“I don’t know that there’s ever been a drug that failed in a large phase 3 program [where] genetic testing identified a potential subgroup that might benefit,” said Dan Rader, a cholesterol expert at University of Pennsylvania, who is an adviser to the company. “This is a grand experiment on a grand scale.”

The risks are daunting. Dalcetrapib is one of a class of drugs called CETP inhibitors that raise levels of HDL, or good cholesterol, and that a decade ago were touted as certain blockbusters in the battle against cardiovascular disease. Pfizer Inc. and Merck & Co., whose cholesterol-lowering drugs called statins transformed treatment of cardiovascular disease, were among four major companies racing to bring CETP inhibitors to the market.

But in 2006, Pfizer’s torcetrapib was found in a major study to increase risk of death and cardiovascular problems, halting its development in a notorious $800 million bust. Roche scrapped dalcetrapib in 2012. Last October, Eli Lilly & Co. killed its program to develop evacetrapib when it failed to reduce risk of major events despite significant favorable changes in cholesterol.

Only Merck’s anacetrapib and a CETP inhibitor Amgen Inc. acquired in a deal last September remain in testing amid broad skepticism that they will succeed.

“It’s been a terrible bust” Eric Topol, a cardiologist and professor of genomics at Scripps Research Institute, La Jolla, Calif., says of the failures. “It’s hard to imagine that there’s just this one gene that pops out to explain the whole story.”

Dr. Topol also said it isn’t clear scientifically why the variant might be beneficial.

DalCor and its allies are optimistic. The DNA analysis study led by Jean-Claude Tardif, director of research at the Montreal Heart Institute, found the favorable gene variant in 20% of patients. Another 40% had the variant associated with a higher risk of heart attacks and strokes. Those with a third variant fell in between. A second study showed the favorable variant was associated with healthier carotid arteries, providing important support for the original findings.

“It was so striking and so concordant we were convinced the chance” of a false result was “very very low,” Mr. Tardif said.

“We wouldn’t be pursuing this opportunity if the signal wasn’t so clear around a single gene,” added Donald Black, DalCor’s chief medical officer and an inventor of Pfizer’s blockbuster statin Lipitor.

Dr. Tardif and Marc Pfeffer, a cardiologist at Harvard-affiliated Brigham and Women’s Hospital, are co-principal investigators of the trial and consultants to DalCor.

The study will enroll patients with an unstable heart condition called acute coronary syndrome—the same type of patient in whom the phase 3 study of dalcetrapib had failed. Half the patients will get dalcetrapib and a statin while a control group will be treated with statins alone. It is likely to be the end of the decade before the results are known.

“Usually with genetics, you have a lot of different genes involved,” says DalCor CEO Robert McNeil.

“When you have something very specific, you say, ‘wow, something is going on here.’”

Founding investors were Sanderling Ventures—which was founded by Dr. McNeil—and Canadian businessman André Desmarais. They were joined by Caisse de dépôt et placement du Québec, the Fonds de solidarité FTQ, and CTI Life Sciences and other undisclosed investors.

Source: WSJ