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With $150M in the bank, Dalcor seeks phase III success with dalcetrapib

By Marie Powers, News Editor

Seeking to succeed where big pharma failed, start-up Dalcor Pharma UK Ltd. completed a $100 million series B round to put an exclamation point on the $50 million series A the company closed late in 2015. The company was launched a year ago by Sanderling Ventures LLC with a new take on dalcetrapib – a phase III asset abandoned by Japan Tobacco Inc. and then by Roche AG after it failed to show efficacy in treating dyslipidemia in patients with coronary heart disease.

Dalcetrapib modulates plasma cholesteryl ester transfer protein (CETP) activity, increasing high density lipoproteins (HDL). Basel, Switzerland-based Roche, which had licensed dalcetrapib from the Japanese pharma, terminated its phase III trial in 2012 after the compound failed to show efficacy.

But Dalcor – the name is essentially a mashup of dalcetrapib corporation – had another take on the asset, based on the work of Jean-Claude Tardif, director of the Research Center at the Montreal Heart Institute (MHI), professor of medicine at the University of Montreal and the Canada research chair in personalized medicine. Research by Tardif published in 2013 suggested that certain genotypes were more likely than others to show a direct benefit from dalcetrapib in reducing cardiovascular (CV) risk.

With colleague Marie-Pierre Dubé, Tardif showed a significant association between the effects of dalcetrapib in altering CV events and the allelic polymorphism at the rs1967309 location in the adenylate cyclase type 9 (ADCY9) gene. Using data from dal-Outcomes – the randomized, double-blind phase III study conducted by Roche that enrolled more than 15,000 patients who were already taking statins for cholesterol control – the researchers showed that patients with an AA polymorphism had a 39 percent decline in CV events compared to placebo while those with the GG variant were associated with a 27 percent increase and those with GA had a neutral effect.

The retrospective analysis of Roche's data was conducted in 5,749 patients and corroborated in a subsequent prospective analysis of 386 patients from Roche's phase IIb dal-Plaque study, which measured change in carotid intima-media thickness (cIMT). As hypothesized, patients with an AA allele showed regression in cIMT while patients with GG progressed.

Those findings whet the appetites of Robert McNeil, a geneticist who founded and serves as managing director of Sanderling, and Fred Middleton, a Sanderling managing director and Genentech Inc. co-founder.

"We said, 'Let's do this,'" and the two went off to talk with Roche, which asked for a $50 million "good faith" commitment before it would negotiate a license, McNeil recalled.

Before taking that step, in 2014 Sanderling convened a group of scientists to review Tardif's data. That move attracted the attention of Canadian business executive André Desmarais, a supporter of the MHI. When the science got a thumb's up, Sanderling and Desmarais put up the $50 million and licensed the oral CETP inhibitor from Roche.

The partners reasoned that, with another $100 million, Dalcor could advance dalcetrapib into a phase III trial in a genetically distinct population of patients with CV disease. They quickly assembled the syndicate, which included founding investors Sanderling and Desmarais as the lead investors together with new investors Caisse de dépôt et placement du Québec, the Fonds de solidarité FTQ and CTI Life Sciences, with participation by additional undisclosed investors.

STATINS 'ONLY PART OF THE STORY'

The series A/B proceeds will take Dalcor "very far down the road," McNeil said, to fund the phase III dal-GenE trial of dalcetrapib compared to placebo, expected to enroll approximately 5,000 patients who recently experienced acute coronary syndrome. An investigational companion diagnostic test developed by Roche Molecular Systems will be used to identify patients for eligibility to enroll in the trial.

"That was part of the deal," McNeil admitted. "[CEO] Severin [Schwan] said, 'You can have the drug, but we're going to provide the diagnostic.'"

Consistent with the trend toward molecularly targeted drug development, he accepted the approach. And, he added, Roche has been a good partner in rebooting the

development of dalcetrapib.

Dalcor expects to initiate the global trial this month, beginning at the MHI, which is serving as the lead academic clinical research organization (CRO).

While the phase III is under way, McNeil is confident that Dalcor will secure a corporate partner to complete clinical development, handle regulatory submissions and commercialize the drug. Although the current investors could ante up more cash, "we think this is a prudent way to approach funding the trial," he told *BioWorld Today*.

In the meantime, the company has organized a management team and assembled national coordinators, sites and CROs for the study. Donald Black, who previously oversaw clinical and regulatory activities for dalcetrapib, was recruited as Dalcor's chief medical officer.

McNeil is keenly aware of the whispers about pursuing a drug that previously failed late-stage studies, but he also believes the understanding of underlying genetics has increased by light years since the investigation of dalcetrapib began, literally, in the last century.

"We think we understand cardiovascular disease," he said. "We do not. We think lowering LDL is a great thing. We've been working on lowering LDL and raising HDL for 35 years, but nothing changed much after statins. Statins are very important. They do rescue a good portion of the population. But they're only part of the story."

McNeil also acknowledged that all of the CETP inhibitors failed, and they raised high-sensitivity C-reactive protein (CRP). Dalcetrapib, he maintained, has the same effect in a certain portion of the genetic population – the GGs – but in the AA group, CRP is down and the candidate produces "a marked, hard endpoint clinical benefit," he said.

That subset could see up to a 40 percent reduction in myocardial infarction, stroke and death, according to McNeil. The phase III study will seek to prove the thesis convincingly.

The trial is expected to take four to five years, and a newly issued patent that incorporates use of the Roche marker provides intellectual property protection to 2034 so Dalcor isn't constrained by a particular filing mechanism.

"We will make sure we're very methodical," McNeil insisted. "We've agreed with our data monitoring board: Do not rush this. We want to make sure we have all of the data solidly in, not some catchy thing which says that after an early look we get to draw a card. If you hold your trial longer by six months, the data package looks much stronger and you can tell which people really should receive this medicine and will benefit from it so that we're not just raising the price of a bunch of drugs to make some money."