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GENOTYPE ONE-IN-FIVE POWER DIVE?

Dalcor CVOT moves along; seek dalcetrapib CETP win with Roche diagnostic test

By Randy Osborne, Staff Writer

With enrollment about six months ahead of schedule, precision medicine specialist Dalcor Pharmaceuticals Inc. has randomized more than 1,000 patients of the expected 5,000 for the phase III dal-Gene trial, a cardiovascular outcomes (CVOT) study of dalcetrapib in patients with acute coronary syndrome (ACS) who have the AA genotype in the ADCY9 gene.

"Obviously, there are obstacles when you're genotyping because you have to screen a lot of patients, but we're actually screening patients at about three times the rate of the dal-Outcomes study, and that seems to be in large part due to the interest in a genetically defined population," the firm's chief medical officer, Donald Black, told *BioWorld Today*. "My original history was with Lipitor [atorvastatin, Pfizer Inc.] 20 years ago, and we had treated a lot of patients who had homozygous as well as heterozygous familial hypercholesterolemia. We see that with other disease states as well: If there's a genetic component, a lot of times that can be an incentive for patients to be part of the study and then also hopefully more compliant to the medication."

Dalcetrapib modulates plasma cholesteryl ester transfer protein (CETP) activity, boosting high-density lipoproteins.

"Five thousand patients for an outcome study is pretty small," Black said. Such experiments have enrolled as many as 32,000. "It's not to be taken lightly," as costs run into the hundreds of millions or billions of dollars, "but the benefits to patients can be very significant as well, as we saw with Lipitor," he added.

Patients have been recruited for dal-Gene at 642 hospitals in 30 countries, including the U.S., and on six continents. The experiment represents the first major test of pharmacogenetically profiling patients to improve prognosis after a heart attack, Dalcor noted. Double-blind, randomized, and placebo-controlled, the multicenter trial will sign up patients recently hospitalized with ACS who express the AA genotype at variant rs1967309 in the adenylate cyclase type 9 (ADCY9) gene, as determined by a companion diagnostic test developed with Basel, Switzerland-based Roche Holding AG.

"If we're successful, [the drug and the test] would both be filed with regulatory authorities," he said.

About a year ago, Dalcor completed a $100 million series B round to supplement the $50 million in series A money secured in 2015. Launched by Sanderling Ventures LLC, Dalcor highlighted a new approach with dalcetrapib, a phase III asset abandoned by Japan Tobacco Inc. and then by Roche after it failed to show efficacy in treating dyslipidemia in patients with coronary heart disease. (See *BioWorld Today*, April 20, 2016.)

Jean-Claude Tardif, director of the Research Center at the Montreal Heart Institute, published research in 2013 suggesting that certain genotypes were more likely than others to show a direct benefit from dalcetrapib in reducing 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 ADCY9 gene. Using data from the dal-Outcomes study – a randomized, double-blind phase III effort by Roche that enrolled more than 15,000 patients who were already taking statins for cholesterol control – the researchers were able to prove 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.

CETP CASUALTIES BUT SURVIVORS, TOO

In heart disease, excitement has been mounting ahead of data due later this month from Thousand Oaks, Calif.-based Amgen Inc. with approved proprotein convertase subtilisin/kexin type 9 (PCSK9) inhibitor Repatha (evolocumab). Detailed data on the 27,500-patient CVOT called FOURIER (Further Cardiovascular Outcomes Research with PCSK9 Inhibition in Subjects with Elevated Risk) will be released at the American College of Cardiology Scientific Session on March 17, but Amgen already has said the study met both its primary and secondary composite endpoints and

that no new safety issues were observed. The primary endpoint comprised time to CV death, nonfatal myocardial infarction (MI), nonfatal stroke and hospitalization for unstable angina or coronary revascularization. Key secondary composite endpoints included time to CV death, nonfatal MI or nonfatal stroke. (See *BioWorld Today*, Feb. 6, 2017.)

"We don't really know what PCSK9 inhibitors will see, but it could very well be that the efficacy seen with dal-Gene is greater for those patients with the right genotype," Black said, which he conceded is "only about one in five" of the population, but the drug, a small molecule taken orally, may bring "some other benefits to patients in the long run as well."

CETP research has "been around for a long time," he noted, with "a number of companies entered into very large programs." Merck & Co. Inc., of Kenilworth, N.J., has anacetrapib in testing. Indianapolis-based Eli Lilly and Co. "appears to have terminated their program with evacetrapib," he said. Amgen is working with a CETP compound gained in the buyout of Naarden, the Netherlands-based Dezima Pharma BV for $300 million up front plus up to $1.25 billion more in development and commercial milestones, as well as sales royalties. "We haven't heard much lately about it," he said. (See *BioWorld Today*, Sept. 17, 2015, and Oct. 13, 2015.)

Another fizzle in the CETP space happened in 2006, when Pfizer Inc., of New York, quit phase III trials with torcetrapib because of mortality rates.

The word on torcetrapib followed news of Pfizer's plan to trim its sales force by 20 percent, due to competitive pressure and the loss of patent exclusivity. Torcetrapib, acquired in the $1.3 billion buyout of Ann Arbor, Mich.-based Esperion Therapeutics Inc., was intended to back up the blockbuster Lipitor. (See *BioWorld Today*, Dec. 23, 2003, and Dec. 5, 2006.)