Evaluate Vantage

March 16, 2018

Interview – Dalcor's Hail Mary pass spirals toward the end zone

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Dalcor was founded with $150m and one mission: to prove that a CETP inhibitor could yet succeed in averting cardiovascular death and complications if only the right patients could be found.

So, when the prominent cardiologist Steven Nissen published an analysis of data from Lilly's pivotal trial of evacetrapib casting doubt on the possibility that dalcetrapib would succeed even in the genetically defined population enrolled into Dalcor's Dal-Gene trial, the spotlight turned to the Canadian company. However, Dalcor executives refuse to let Dr Nissen's work shake them, pointing to differences between Lilly's project and theirs.

"Because so many things die in pharma it's easy to be a sceptic," Don Black, the company's chief medical officer, tells *EP Vantage*.

But he admits that the Dal-Gene trial is "probably" not fully funded to completion, raising questions about the ethics of running it. While Mr Black says Dalcor has received assurances from its investors that they will provide more financing if necessary, the latest data, which come down against Dalcor's hypothesis that dalcetrapib could work in a particular genetic subtype, might make this rather hard.

If any interim analyses are capable of suggesting futility in Dal-Gene, Dalcor will be faced with a near-impossible task: going to investors for more cash to fund a failed trial that, for ethical reasons, it must run to completion.

The other cholesterol

CETPs – cholesteryl ester transfer protein inhibitors – were tested as a way of preventing heart attacks and strokes by raising HDL cholesterol, which scavenges the LDL cholesterol that forms atherosclerotic plaques and transports it to the liver to be metabolised.

In spite of CETP inhibitors' potency in raising HDL, pivotal outcomes trials in more than 40,000 patients showed that, broadly speaking, they were either ineffective at preventing myocardial infarctions, cardiovascular death or other complications, or were of limited benefit. The last to read out was a trial of Merck & Co's anacetrapib, whose meagre 9% reduction in cardiovascular events was later traced to its LDL-lowering effect (*ESC 2017 – Merck still won't Reveal its hand, August 29, 2017*).

Dalcor was created to follow a retrospective finding in the Dal-Outcomes trial of Roche's dalcetrapib that patients with a specific genetic polymorphism – the AA variant at rs1967309 in the ADCY9 gene – had a 39% reduction in cardiovascular events. Patients with the GG variant at the same position had a 28% increase in events.

This is an intriguing finding, although even the chief investigator of Dal-Gene, Jean-Claude Tardif of the Montreal Heart Institute, acknowledges that it is not clear how the gene is linked to cardiovascular responses to dalcetrapib.

One of Dr Nissen's points when he presented his analysis at the recent American College of Cardiology meeting was that genome-wide association studies now commonly conducted on large outcomes trials can lead to therapeutic insights but can also create "false discovery".

"His view is this could still be chance," Mr Black says. "I completely understand Dr Nissen's view of the data. It's the sort of glass half-full or half-empty."

Maybe, maybe not

The glass-half-full view is what has sustained Dalcor as a company, of course, but Dr Nissen's analysis should be taken seriously. He reviewed data from the Accelerate outcomes trial of Lilly's evacetrapib, comparing the rates of cardiovascular complications in patients on active drug and on placebo in three genotypes at rs1967309 in the ADCY9 gene: AA, AG and GG.

AA patients taking evacetrapib were 12% less likely to have experienced an adverse cardiovascular event than those taking placebo, a finding that yielded a nominal p value of 0.06; when adjusted for cardiovascular risk factors like smoking status the benefit shrank to 7%.

Moreover, Dr Nissen pointed to a small number of events – 38 in a trial that enrolled 15,865 people – that yielded the genetic connection in the dalcetrapib Dal-Outcomes trial. Yet he acknowledged that differences in the potency of the two drugs or in the populations – dalcetrapib was tested in patients with recent acute coronary syndrome while evacetrapib's trial had patients with more chronic high-risk vascular disease – could mean dalcetrapib's benefit is real.

This is what Dalcor leans on. "We do think there are enough differences in the drug and the study design," Mr Black says.

Precision medicine

The Dal-Gene study should put the argument to rest. It will enrol 5,000 patients with recent acute coronary syndrome to take either dalcetrapib or placebo in addition to LDL-lowering medication, with a target level of under 100mg/dl. Mr Black says the trial is 85% recruited and should complete enrolment by mid-year, putting it on track to read out in 2020; the primary endpoint is a composite of cardiovascular death, or non-fatal myocardial infarction or stroke.

The readout is about as binary as it comes in biopharma. Success could make dalcetrapib into the sort of cardiovascular product payers like these days, with a tightly defined population and a benefit on a hard outcome. Failure would see a definitive end to CETP development, more than 20 years after the first project in this space was first tested in humans.

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