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ACC – All eyes on Merck as evacetrapib data underwhelm

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Merck & Co's last-chance bet on anacetrapib rests largely on numbers. By enrolling twice as many heart disease patients in clinical trials as any previous project with this mechanism of action, the company seems to be counting on teasing out a benefit that its rivals in the CETP inhibitor class could not.

The latest failure was Lilly's evacetrapib, and the full data from its pivotal Accelerate trial should not lend much confidence that Merck's pill will generate statistically significant or even a clinically meaningful reduction in cardiovascular death or hospitalisations. The findings could even be taken as a hint that the cholesterol-lowering effects of the new PCSK9-targeting drugs Praluent and Repatha will fail to generate positive long-term outcomes.

No benefit

Accelerate's data-monitoring committee terminated the trial last October because it was unlikely to meet its primary endpoint, a composite of cardiovascular death, myocardial infarction, revascularisation or unstable angina, in high-risk patients.

At the American College of Cardiology meeting Accelerate's lead investigator, Dr Stephen Nicholls of the Royal Adelaide Hospital, revealed a virtually identical event rate on that primary endpoint: 774 for patients taking evacetrapib and 768 for those on placebo 36 months after randomisation. Patients in the trial had to be taking a statin in addition to their assigned medication unless they were intolerant to or contraindicated for statins.

This near-identical event rate came despite biomarker improvement: namely, a significant 37% average decrease in the low-density lipoprotein (LDL) cholesterol that leads to atherosclerosis, along with a 130% average increase in the high-density lipoprotein that helps remove LDL particles from the walls of blood vessels. Despite this, Accelerate was a miss on all secondary endpoints, with only all-cause mortality approaching significance.

This marks the third phase III failure of a pill from the cholesteryl ester transfer protein (CETP) inhibitor class, following Pfizer's torcetrapib nearly a decade ago and Roche's dalcetrapib in 2012. It also leaves a key safety question unanswered, as it did not put to rest the worry that the high blood pressure that helped derail torcetrapib might be an off-target class effect. Evacetrapib patients experienced a small but significant average rise of 0.9mm Hg in systolic blood pressure.

What is more, this trial only adds to the worry that lowering of LDL beyond what can be accomplished with statins can show no long-term benefit. This should be of some concern to Sanofi/Regeneron and Amgen, which have the cholesterol-lowering PCSK9 injections Praluent and Repatha in outcomes studies that will affect their eventual uptake. Pfizer just reported its first positive phase III data for its own PCSK9, bococizumab, so it will also be paying attention.

Taking the evacetrapib data together with the two failures that preceded them, analysts from Bernstein Research and Leerink concluded that Merck's Reveal trial of anacetrapib does not have much of a chance when it reads out next year. Leerink is alone in forecasting any revenue from this project, forecasting sales of $220m in 2020.

Bigger numbers

Yet Merck thought that the opportunity was weighty enough to plough hundreds of millions of dollars into Reveal, which has a planned enrolment of 30,000. The size of the trial, double that of dalcetrapib's dal-Outcomes trial and nearly triple that of Accelerate, gives some reason to hope that what appeared to be positive trends in earlier CETP studies can actually meet statistical significance.

But is this reason to hope? At three years of follow-up, evacetrapib showed no signs of the statistical "separation of the curves" that investigators would hope to see if a larger trial were to succeed in terms of the primary endpoint. Moreover, the one endpoint that generated something that looks like a statistical near-significance, all-cause mortality, was dismissed by Bernstein analyst Tim Anderson as "probably not real".

Dr Nicholls acknowledged “confusion” about the CETP disappointment and said investigators were “trying to understand how a drug that seems to do all the right things” has no long-term effect on cardiovascular health. Merck has made a pretty big bet on a mystery – it needs to hope that anacetrapib solves it.

Trial name	ID
Accelerate	NCT01687998
Reveal	NCT01252953

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