

Event - Merck awaits news on free win with high risk heart drug



Amy Brown

The cardiovascular world might have moved on from CETP inhibition, but for Merck & Co this remains a very expensive investment. In the next couple of months the huge 30,000-patient Reveal trial of anacetrapib will read out, and many expect the data finally to lay this mechanism to rest, at least in the broad population.

This lack of belief is rooted in the failure of three previous agents to reduce the risk of heart attacks in phase III, although some hang on to hope that anacetrapib's strong effect on lowering "bad" cholesterol will tease out a signal. Should this emerge, seemingly against the odds, the project will be viewed as a free win for Merck. Conversely, with so much attention on the company's oncology efforts, failure will be easily shrugged off.

Product	Anacetrapib
Company	Merck & Co
Product NPV	\$1.8bn
% of mkt cap	1%
Event	Phase III data
Due	Q1

Consensus for sales in 2022 stands at \$543m, according to *EvaluatePharma*, a figure that will be highly risk-adjusted and probably not reflective of the drug's potential, should the trial read out positively. Back in the CETP inhibitor heyday, before the likes of dalcetrapib and evacetrapib had failed, these agents were touted as future blockbusters; given payer power these days, that label cannot be pinned on a primary care drug with such free abandon.

In any case the medicine cabinet looks different now with the anti-PCSK-9 antibodies available for those patients unable to control their cholesterol with statins alone. Not that many people are getting them - the price tags of Repatha and Praluent are severely restricting their patient pool, pending data from their own cardiovascular outcome studies.

Merck will be in a very interesting position should anacetrapib triumph - regardless of whether the anti-PCSK-9s fail or win in their own outcome trials - particularly as it looks like Praluent is shortly to exit the US market.

Revealing all

These machinations will be irrelevant, of course, if Reveal fails.

In the trial patients who already have some form of circulatory disease have been given atorvastatin plus anacetrapib or atorvastatin plus placebo, and tracked for hearts attacks, revascularisation procedures or death from coronary heart disease. The primary endpoint is a composite of those measures; secondary endpoints split these out and also include stroke, among other cuts of the data.

Safety signals are not expected given earlier data, although blood pressure will be closely watched - this derailed torcetrapib a decade ago, and both dalcetrapib and evacetrapib were seen to raise blood pressure, albeit marginally. This has been posited as a reason why these agents do not confer a cardioprotective benefit.

These drugs were originally pursued for the ability aggressively to raise levels of HDL cholesterol, which removes harmful inflammatory particles from the walls of blood vessels, but it is now believed that they convey their apparent benefit by lowering LDL cholesterol, which leads to atherosclerosis.

But three drugs have now established that this mechanism of action has no impact on cardiovascular events,

most recently evacetrapib, which had the most marked effect on these lipid measures ([ACC – All eyes on Merck as evacetrapib data underwhelm](#), April 4, 2016).

CETP inhibition - last chance saloon?							
Product	Company	CVOT study	Enrollment	Outcome	LDL lowering	HDL raising	NCT ID
Torcetrapib	Pfizer	Illuminate	15,067	Stopped in 2006 for safety	-25%	+70%	NCT00134264
Dalcetrapib	Roche	Dal-Outcomes	15,865	Stopped in 2012 for futility	minimal	+35%	NCT00658515
Evacetrapib	Eli Lilly	Accelerate	12,092	Stopped in 2015 for futility	-37%	+130%	NCT01687998
Anacetrapib	Merck	Reveal	30,624	Ongoing	?	?	NCT01252953
Dalcetrapib	Dalcor	Dal-Gene	5,000	Ongoing	?	?	NCT02525939

It is hard to escape the conclusion that these relative lipid movements are irrelevant to long-term outcomes. And although the Reveal study is testing the same mechanism of action in larger numbers, and in 2015 it passed its last test for futility, a positive outcome would be a huge surprise to the cardiology and financial worlds.

Some believe that the CETP inhibitors do have a future. Roche's dalcetrapib found a new home with Dalcor, which remains convinced that a genetically defined subgroup of patients who showed a strong benefit in Dal-Outcomes could emerge as a target audience. The company recently started a 5,000-patient study to test this hypothesis ([Dalcetrapib goes to new home with focused clinical strategy](#), June 9, 2015).

Should mixed messages emerge it seems unlikely that Merck will be willing to countenance further study. The company is a fading cardiovascular giant with former mega brands Vytarin, Zetia and Zocor all in decline, and surely only an unequivocally positive signal will persuade it to take this drug to the regulators.

For big pharma, CETP inhibition could be over with anacetrapib.

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