Evaluate Vantage

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AHA 2010 – Benefits of Merck's HDL booster could be revealed by 2014

Amy Brown

Following the release of well-received results from the Define trial of anacetrapib at the American Heart Association (AHA) meeting, Merck & Co wasted little time by simultaneously announcing a massive 30,000 patient trial of the drug, dubbed Reveal, to be managed by the Clinical Trial Service Unit at Oxford University in the UK.

The steering committee for the study will be chaired by Professor Rory Collins of Oxford University, and speaking on the sidelines of the AHA meeting he tells *EP Vantage*such a large trial is a minimum requirement to generate the kind of compelling evidence of the drug's efficacy and safety. Expected to start in April 2011, the trial is designed to last six years, although Professor Collins says there is chance it could be stopped in 2014 if the data is "stunningly effective across a whole range of outcomes". More good news for Merck given it is playing catch-up to Roche's dalcetrapib, which could be filed in 2014.

Large undertaking

Men and women over 50 years old with a history of cardiovascular disease will be enrolled in the placebo-controlled trial. All patients will be given Lipitor to ensure good control of LDL, or 'bad cholesterol', and then randomised to receive anacetrapib or placebo for at least four years.

Primary outcomes include rates of death from coronary heart disease, heart attacks and revascularisation procedures. However, Professor Collins says the size of trial means it may be possible to also assess much harder clinical endpoints, such as non-fatal myocardial infarction and total mortality rates.

Given the experience with Pfizer's torcetrapib, strict safety monitoring will also be critical, especially as enrolment escalates. Particular attention will be paid to patients in whom LDL drops to ultra-low levels, given the effect from such a dramatic reduction in LDL is still unknown. In the Define trial patients were taken off anacetrapib if their LDL dropped below 25mg per decilitre, which occurred in 142 patients receiving the drug, or 17.6% of treated patients.

Another aim of Reveal is to generate the data required to properly assess the drug's affect on sub-groups of patients, such as men and women, diabetics and those with hypertension.

"When you think of all this, is 30,000 enough? Probably not", says Professor Collins in terms of whether Reveal will be able to answer all these questions definitively.

Early look

Although the overall intention is to treat patients for four years, the steering committee will be reviewing the safety and efficacy data after at least two and a half years from the median point, or from the 15,000th patient being treated.

This could occur in 2014 and Professor Collins says if the efficacy benefit and safety data is better than has been estimated in designing the trial, there may be a case to stop it early.

This would be a bold move, given some criticism of the Jupiter trial with Crestor which was stopped early but has left some important questions unanswered. And as Professor Collins points out, once you stop a trial there is no going back and seeing if the drug works in certain sub-groups, for example.

Conversely, if the trial takes its full course, which has to be the assumption at this stage, Merck will have to wait until 2016 or early 2017 before completion.

Cost-effective

Another key aspect of the Reveal trial that Professor Collins was understandably keen to impress is its

relatively low cost, compared to the ongoing study of dalcetrapib in 16,000 patients and other large scale trials.

“We have tried to streamline it so it can be done at modest cost”, says Professor Collins who claims the infamous Illuminate trial of torcetrapib cost $400m and the recently-completed Rocket-AF study of Xarelto cost $500m.

In contrast, despite enrolling almost double the amount of patients, Professor Collins estimates that Reveal will be, “of the order of a few hundred million dollars”. Oxford University has been given a grant of £96m which Professor Collins says will cover a large proportion of the study, outside of local coordinating costs in North America and Scandinavia.

Differing strategies

Since the fall-out from torcetrapib, the contrasting strategies of Merck and Roche in developing their CETP inhibitors has been intriguing.

Whereas Merck took a more conservative approach with the Define trial, mainly to address safety concerns, Roche jumped straight into a large-scale trial to assess clinical outcomes, which is ultimately what regulators will need to see before approving either candidate.

Dr Robert Eckel, professor of medicine at the University of Colorado, believes there is merit in both strategies, although seems more sympathetic to Merck’s approach. “Merck historically has been a conservative company in terms of drug development and clinical trial design; from a scientific perspective I think most of us favour that type of approach”, says Dr Eckel.

However, given the obvious disparity in trial sizes between Reveal and Roche’s dal-Outcomes trial of 16,000 patients, Dr Eckel believes that the Roche trial may be adequately powered to generate sufficient outcome data. Conversely, “the Reveal trial may be overpowered if this effect on lipids is as much as they have demonstrated here today”, says Dr Eckel.

Either way, the proof will be in the pudding. For Merck it may have to wait a little longer to eat it, but at least the company is not paying over the odds.

And if CETP inhibitors do finally have their day, the size and scope of the statin of market – which was worth $23bn at its peak – indicates there will be ample room for a couple of competitors, which could expect to reap significant commercial rewards.