Evaluate Vantage

May 08, 2012

Roche’s dalcetrapib failure not end of the road for CETP

Amy Brown

If any of the three CETP inhibitors in late stage development was going to fail on efficacy grounds, Roche’s dalcetrapib looked the most likely candidate. Bestowing a relatively benign boost to HDL levels and having little impact on LDL compared to Merck & Co’s and Eli Lilly’s compounds, the potential for the pill to show little clinical benefit was always there.

While not an encouraging sign for others in the class it does not mean they are now destined to fail. It also certainly does not disprove the HDL hypothesis - that by boosting levels of good cholesterol heart attacks and strokes can be prevented. Researchers have appreciated for some time now that HDL is far more complicated than a simple higher is better approach, something that Roche acknowledged in its justification for pushing forward with dalcetrapib in the first place. However, the failure is still disappointing, and a setback to attempts to harness the power of a seemingly potent cardio-protective molecule.

Greater insight

Other than saying that the dal-Outcomes study was stopped after a second interim analysis showed no sign of clinically meaningful efficacy and that no safety signals were seen, Roche has yet to reveal any more details about its findings.

Despite the disappointing ending researchers working in the HDL field will no doubt be hoping that full data and analyses emerge, as much remains unclear about the role of this particle and how it works (*Vantage Point - Functionality in focus as HDL hypothesis awaits confirmation, September 8, 2011*). The failure of torcetrapib, Pfizer’s CETP inhibitor that was abandoned for safety reasons, spurred much of the work into HDL functionality that drives the field today and the large dalcetrapib programme Roche was conducting will have much to contribute.

Looking on nervously will be Merck, which has already started a huge 30,000 patient outcome study with anacetrapib, and Lilly, which signalled last year that its candidate evacetrapib would be entering phase III (*AHA 2011 - CETP sweet spot in focus as third contender heads for phase III, November 16, 2011*).

Given the huge cost of a pivotal programme it would not be surprising to see Lilly delay this decision further, possibly until Merck reports progress or otherwise with anacetrapib. News from Merck is unlikely to emerge this year, however, meaning Lilly will need to work hard to convince R&D-weary investors that the risk is worth taking at this stage, if it does decide to push on.

Still succeed?

Given the different attributes of these drugs and the impact they have on lipid profiles, it remains possible that anacetrapib and evacetrapib could still succeed.

All work by inhibiting CETP, or cholesteryl ester transfer protein, which is involved in the shuttling of cholesterol between lipid carrying particles like LDL and HDL. This mechanism is called reverse cholesterol transport and CETP is thought to play a vital role in the system that ultimately removes cholesterol from cells throughout the body, including the walls of arteries, to the liver for excretion.

Blocking CETP’s function boosts HDL levels and, developers hope, ultimately helping to prevent heart attacks and strokes. However, while anacetrapib and evacetrapib appear to more than double HDL blood levels dalcetrapib was shown to boost levels by only a third. At the same time, the Merck and Lilly drugs also lower LDL, while the Roche candidate was benign on this measure.

The Swiss pharma giant was undeterred by this seeming lack of potency, describing dalcetrapib as a CETP modulator rather than an inhibitor like the others in the class. Instead of freezing the system of cholesterol transfer, which is essentially how torcetrapib acted and possibly the other two agents, dalcetrapib allowed the remodelling of HDL to continue, facilitating reverse cholesterol transport and the production of functional HDL particles, Roche argued.

Raising stakes

At this stage it is unclear whether Roche’s theory about CETP modulation was flawed or dalcetrapib simply not up to the job. Both a very potent - torceptrapib - and seemingly less potent - dalcetrapib - CETP inhibitor have failed, meaning the linear relationship between CETP inhibition and cardiac outcomes, if indeed there is one, remain unexplained.

And although Roche was clearly cognisant of the importance of HDL functionality over simply raising measurable levels in the bloodstream, this was not enough to generate success.

HDL functionality itself has yet to be fully understood, what functional HDL looks like or how it can be measured, and indeed what role this diverse family of particles plays in processes such as inflammation, coagulation and oxidisation, all of which are likely to be tied to the particle's cardioprotective properties. It will no doubt be many years before this is unravelled. In the meantime, the field could do with a success story to confirm that researchers are at least on the right track with the HDL hypothesis.