Evaluate Vantage

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Resverlogix doomed by second failure

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Resverlogix might still be mulling whether its HDL-booster RVX-208 has a future, but investors have already made up their minds. The failure of a second large phase II study caused shares in the Canadian company to crater 93% yesterday, erasing $215m from its market value and surely signaling the end of the heart project.

Little information was given in the press release other than that the trial, looking at artery plaque regression, had failed to hit its primary endpoint. Surprisingly for a study using a hard endpoint measured by ultrasound, the company pointed the finger at an unexpectedly high placebo response. Greater detail is needed to fully understand this observation. But for Resverlogix and others desperately searching for support of the HDL hypothesis, it seems RVX-208 is not a source of hope.

Success not assured

The phase IIb Assure study recruited 324 high-risk cardiovascular patients with low HDL, so-called "good cholesterol", who were given either RVX-208 or placebo twice daily for 26 weeks. The primary endpoint was change in percent atheroma volume, a measure of artery plaque, determined by intravascular ultrasound (IVUS).

Patients who received the agent had -0.4% plaque regression from baseline, giving a p value of 0.08. A change of -0.6% or greater was needed for the study to succeed. The trial met its secondary endpoints, including regression of total coronary atheroma volume and increases in HDL and Apolipoprotein A-I (ApoA-I), a precurser of HDL. No further details were provided, other than a mention of an “unexpected strong placebo result”.

This is not the sort of trial where a placebo effect should influence the outcome – this finding is more likely to be due to trial design or recruiting the wrong patients. Resverlogix said it would spend the next few months analysing the full data to determine whether continued development of RVX-208 is warranted, but further work will be incredibly hard to justify after this second clinical failure.

Big backing

Resverlogix did press on in the face of adversity after the first setback, and the outcome of the Assure study looks very familiar to the situation in which Resverlogix found itself almost three years ago, when it unveiled what could generously be described as mixed results from the Assert study (*AHA 2010 – Resverlogix falls back to earth, November 18, 2010*).

Assert failed to hit its primary endpoint of a statistically significant increase in ApoA1, although the highest of three doses tested came very close. Secondary endpoints of HDL raising and increases in large HDL particles were met in the two highest doses. The most worrying signal that emerged from Assert was elevated liver enzymes - the company put this down to a sign that the drug was working but the issue was undeniably another red flag alongside the efficacy concerns.

The ongoing development of RVX-208 was backed by some big names in cardiology and this no doubt helped Resverlogix push on where others might have stalled. The Assure trial was led by the Cleveland Clinic and the clinical steering committee counts Steven Nissen as its chairman and Stephen Nicholls as its principle investigator.

Unlocking the secrets

These researchers found enough in the data previously to push on with RVX-208 and, whatever the ultimate decision about the project, they will no doubt find glimmers of hope in the Assure data. But a lot has happened in the HDL space since the Assert failure. A second CETP inhibitor, Roche’s dalcetrapib, has fallen, and more recently the huge Thrive study with Niacin failed to establish a benefit for that HDL boosting therapy (*Tredaptive fails to thrive in huge outcome study, December 21, 2012*).

It is now widely accepted that a ‘higher is better’ approach to HDL is simplistic – the functionality of the molecule for example is much more important (*Vantage Point - Functionality in focus as HDL hypothesis awaits confirmation, September 8, 2011*). RVX-208 works by boosting production of ApoA-I which, according to

Resverlogix, should help create new particles of HDL that are highly active in pulling cholesterol out from atherosclerotic plaques.

However, doubts that the modest efficacy seen in Assert would translate into a measurable benefit in Assure appear to have been well founded. Whether this is down to a failure of the molecule or a failure of the hypothesis remains unclear, but RVX-208 is now likely to be considered a dead end. Hopefully researchers will still be able to glean something from these efforts to help finally unlock the secrets of HDL.

Trial name	Trial ID
Assert	NCT01058018
Assure I	NCT01067820

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