Evaluate Vantage

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EP Vantage Interview - Cerenis adds €40m to the HDL debate

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Cerenis Therapeutics announced one of the largest European financings so far this year yesterday, raising €40m ($52m) in a series C round. The cash will mostly go towards starting a large phase II trial of its lead compound, CER-001, a novel HDL-mimetic which the company believes could prove effective at preventing repeat heart attacks in patients with a recent history of coronary problems.

Although the therapeutic benefits of raising HDL – so-called good cholesterol – are certainly becoming more widely appreciated, a broader debate continues to rumble on. Only last week, *The Lancet*published a new analysis of AstraZeneca's Jupiter study which questioned the relevance of HDL levels in patients with low LDL. Add to this the fact that developing agents that can boost HDL safely has proved a huge challenge, and that Cerenis has recently managed to attract the former head of GlaxoSmithKline, Jean-Pierre Garnier, to its board, and it seems the French company's progress will be watched with great interest.

Careful interpretation

While a high LDL to HDL cholesterol ratio can lead to the build up of damaging arterial plaque, the opposite is thought to be true when the ratio is flipped. This is because HDL stimulates the reverse lipid transport system, used by the body to clear plaque through the liver. Hence the use of HDL-boosting therapies such as Abbott Laboratories' Niaspan (niacin), which have been proven to lower the risk of coronary events, and are often used in combination with LDL-lowering statins.

Still, when and how these therapies should be used remains a big issue. The analysis published in *The Lancet*last week concluded that HDL levels were not predictive of the risk of a cardiac event among patients treated with Crestor who had attained very low concentrations of LDL cholesterol. The authors wrote, however, that measuring HDL is still useful as part of initial cardiovascular risk assessment, and added that finding out whether raising HDL cholesterol improves cardiac outcomes after taking statin therapy remains a very important issue.

Jean-Louis Dasseux, co-founder and chief executive of Cerenis, believes that because patients in the Jupiter trial had very low levels of plaque anyway, these results need careful interpretation.

"There was nothing wrong with what was written in this study, but to better see the effect of HDL raising the patient population needs selecting carefully," he tells *EP Vantage*. "The Arbiter 6-Halts study was very encouraging because what they demonstrated was that could HDL could be increased, and a clinical benefit seen."

Arbiter 6-Halts, a study that pitted Abbott Laboratories' Niaspan against Merck & Co's Zetia, which works by lowering LDL levels, was stopped early after patients seemed to be fairing much better in the niacin arm (*Abbott should benefit from direction of cholesterol debate, November 16, 2009*).

Natural mimic

Either way, Mr Dasseux remains convinced that as the most potent anti-inflammatory molecule in the body the therapeutic benefits of raising HDL levels are clear, particularly in the patient population that will be enrolled for the phase II trial of CER-001.

CER-001 is based on natural apolipoprotein A-I (ApoA-I) the major structural protein of HDL. Its target audience will be patients who have suffered their first heart attack; these patients are at heightened risk of second or third attacks, as more plaque breaks away from the artery walls.

In the phase II trial, the company will seek to prove that an infusion of CER-001 after a coronary event, and after a patient has been treated with anti-platelet therapy, can rapidly and effectively remove large amounts of plaque, by triggering reverse lipid transport.

"We want to show we can significantly reduce plaque compared to both baseline and placebo, and can regress artherosclerosis," Mr Dasseux says.

Full details of the trial are still under wraps, but the company will be using intravascular ultrasound to measure effectiveness.

Story worth following

Mr Dasseux believes Cerenis has overcome many of the problems encountered by previous attempts to develop HDL mimetics, with a novel manufacturing technique. The company believes it now has a commercially viable, safe drug, and will strive to prove this over the next year or so. High profile failures in this space, such as Pfizer's torceptrapib, means many will be sceptical until more data are available.

At the same time, Cerenis is also working on products that can be taken longer term to raise HDL. The side effects of niacin, which causes such severe flushing and itching that a huge proportion of patients stop taking the medication, means there is a need for alternative therapies.

CER-627 is a fixed-dose combination of niacin and slow-release aspirin which could provide an answer. The compound is ready for phase II trials and Cerenis is in the process of looking for a partner.

As for CER-001, the company seems keen to generate proof of concept in house before finding a partner. The €40m raised will help in this regard, although Mr Dasseux points out that a second closing on the round, due soon, should see that figure rise.

The presence of Mr Garnier, the former head of GlaxoSmithKline who recently finished a two-year stint as chief executive of Pierre Fabre, should certainly help open doors for future financing and partnering talks. With cardiovascular disease remaining a hot area for big pharma, Cerenis looks like a story worth following.