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Thought CETP inhibition was dead? Think again

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New Amsterdam wants to prove that the ill-fated mechanism has a role in cardiovascular disease – and this time it’s all about the bad cholesterol.

The failure of CETP inhibitors to prove themselves as a treatment for cardiovascular disease must rank as one of the biggest, and costliest, R&D disappointments of the past 20 years. With them died the HDL hypothesis: that heart attacks and strokes could be prevented by hiking levels of so-called “good” cholesterol.

Armed with a $200m series A round and Amgen’s unwanted CETP inhibitor obicetrapib, New Amsterdam is embarking on a revival of the mechanism, but this time focusing on LDL reduction. “There was an enormous enthusiasm to develop this drug from a financial and business point of view,” says the company’s founder and chief scientific officer, John Kastelein, telling *Evaluate Vantage* that a second funding round was already in the works.

The series A was only done in January 2021, led by the venture firms Ascendant BioCapital and Morningside, but more cash will be needed to complete two large clinical studies. Dr Kastelein estimates that Prevail, a cardiovascular outcome study seeking 9,000 subjects, will cost $150-200m, but declined to say how funds might be raised.

The clinical programme under way is designed to win approval for obicetrapib in a secondary prevention setting – to reduce the risk of heart attacks or strokes in people with established cardiovascular disease. Success would put the project on a similar footing to mechanisms including PCSK9 inhibitors, which are known to be very effective at lowering LDL.

Cheap statins are always the first option when cholesterol needs lowering, but many people fail to get as low as advised. The high price of PCSK9s means that they are not used as widely as they should be, Dr Kastelein maintains. This is where New Amsterdam sees obicetrapib coming in.

“We will have a drug priced according to the health economic benefits it gives,” he says. “30 million people in Europe, the US and Japan need additional LDL lowering. We don't want to end up with prior authorisations, paperwork, and people that hate us because they think we're greedy.”

Proving the point

First obicetrapib needs to prove itself in the clinic, and Mr Kastelein believes that the project will be as effective as PCSK9s. The completed phase 2b Rose trial found a 51% reduction in LDL cholesterol in obicetrapib-treated patients already on high-intensity statin therapy – a result that makes the CETP inhibitor “just as potent” as Novartis’s PCSK9 drug Leqvio, he says.

The Broadway and Prevail trials are intended to confirm this in substantially more patients. The former is primarily measuring LDL and should read out early in 2024. Prevail should follow with data in early 2026.

Given CETP inhibition's history, approval ahead of outcomes data cannot be assumed. However, Dr Kastelein argues that much of the past disappointment can be put down to mistakes made with the class's development. Some were his own, he admits – he was involved in many of the failed clinical programmes.

Of the now-abandoned projects, Pfizer's torcetrapib is an exception – something the FDA has acknowledged, he says – in that it had a unique off-target blood pressure impact that caused more problems than it prevented.

The drawback of Roche's dalcetrapib was that it had no impact on LDL, albeit hiking HDL levels by around 30%, which is now known to do nothing to a person's cardiovascular risk profile. "Raising HDL is just a cosmetic thing that you see in your plasma," Dr Kastelein says.

Lilly made two big mistakes with evacetrapib. A previously untested dose was taken into phase 3 and the project's LDL-lowering capacity was overestimated, meaning that the pivotal study was underpowered, and it failed.

Hitting the target

The final CETP outcome study to report was Reveal, which investigated Merck & Co's anacetrapib. Although this was a technical success, it found an underwhelming 9% reduction in major adverse cardiac events (Mace). Anacetrapib was abandoned after it was also found to have a very long terminal half-life.

Anacetrapib's real potential only emerged in long-term follow-up data, published last year. This described how Reveal's 9% Mace reduction improved to an impressive 20% after 6.5 years.

Dr Kastelein maintains that the Reveal results finally validated the CETP mechanism. However, even if New Amsterdam is proved right clinically, there will be many commercial challenges facing obicetrapib. Not least of these must be a short patent life: the project first went into the clinic in 2008. The company claims to have "10+ years" of exclusivity.

Still, Dr Kastelein insists that obicetrapib has the optimum characteristics for a CETP inhibitor: a short half-life, potent LDL lowering and no off-target effects.

"There's been a lot of new data in the last two years … that made us decide to pick this drug up and do it again, but this time do it right," he says.

This article has been amended to correct the lead investors in New Amsterdam's Series A round.