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Esperion and PCSK9s set the stage for cholesterol-lowering showdown

Jacob Plieth

With another positive study under Esperion's belt the next piece of the bull case for the company is in place, setting the stage for what looks to be a turnaround year for cholesterol-lowering therapies.

Fundamental to this will be Amgen and Sanofi/Regeneron's duelling anti-PCSK9 antibodies, which over the weekend posted safety data that strengthened the case for their US approval, even though investors are no closer to determining which might be better. The upshot for Esperion is that the takeover thesis is alive and well, even with the stock up 467% over six months.

The big question remains when any of these therapies might be approved in the broad patient population – something that likely still hangs on large cardiovascular outcomes trials. Hence the initial focus on smaller patient groups: statin intolerants for Esperion's ETC-1002 and those with familial hypercholesterolaemia for the PCSK9s.

Esperion had already rewarded the faith of IPO investors when last October ETC-1002 beat Zetia in a study of 348 patients, half of whom were intolerant to statins – setting up the drug's initial route to market. Today's trial in 134 patients shows the oral project also to be efficacious when added on top of statin therapy.

The latest data were impressive since patients were already stable on statins. While placebo recipients saw a mean 4% reduction in LDL cholesterol from baseline, the lowering effect was 17% for 120mg and 24% for 180mg of ETC-1002 ($p=0.0055$ and <0.0001 respectively), suggesting a dose response as well as hitting the primary endpoint.

The focus now turns to a third phase II trial, which tests ETC-1002 monotherapy in patients with high cholesterol and hypertension and should read out in the second quarter. Investors will also eagerly await news of the design of phase III, now that an FDA hold has been lifted (*On to phase III for Esperion as FDA lifts hold, February 05, 2015*).

While Esperion's initial focus thus remains on statin-intolerant patients, the company was clear that today's data were all about the bigger opportunity – the "much broader potential than Esperion on its own would want to move forward", in the words of the group's chief executive, Tim Mayleben, on a call.

Neck and neck

A key consideration will be US FDA verdicts on the PCSK9s – Sanofi/Regeneron's Praluent and Amgen's Repatha. With efficacy running at around a 60% LDL-lowering effect for both, the two are neck and neck.

The Sanofi/Regeneron project has a PDUFA date of July 24, while the FDA is due to act on Repatha by August 27. It is possible that both will be reviewed at the same advisory panel meeting, meaning that the race to become the first marketed anti-PCSK9 MAb in the initial narrow indication is too close to call.

As for broader use this of course depends on two massive cardiovascular trials – Praluent's Odyssey Outcomes and Repatha's Fourier. Though formally these are not due to read out until 2017/18 there are growing hopes that they might be halted early for efficacy.

And analysts have been quick to jump on additional safety data – concerning major adverse cardiovascular events in the Odyssey Long Term and Osler 1 and 2 studies – presented over the weekend at the American College of Cardiology meeting.

"It was expected that both drugs would show cardiovascular benefits [but] the magnitude still comes as a surprise," wrote Leerink analysts. Events were seen in 1.7% of patients on Praluent, versus 3.3% of placebo recipients, and in 0.95% of Repatha patients versus 2.18% for placebo.

Of course the numbers are tiny – just 60 events in total for the Repatha studies and 53 for Praluent – so the data are ultimately inconclusive. Nevertheless, with hazard ratios in the 0.5 region for both analyses the sellside thinks the results increase the chances of both drugs showing an elusive cardiovascular benefit in their

outcomes trials.

Ultimately the battle could be determined by marketing muscle and pricing rather than safety and efficacy, and it is Esperion's ETC-1002 – an oral molecule – that could really upset the pricing assumptions for the subcutaneously injected anti-PCSK9 MAbs. Still, this scenario will not play out for a while yet, and in the meantime Esperion must find a partner to fund its own huge cardiovascular programme.

Its stock opened up 16%, so investors clearly think a licensing deal or even takeover – say by Pfizer, Lilly or AstraZeneca – could be on the cards. FDA decisions on the PCSK9s could focus the minds of those looking at Esperion.

Project	Study	Design	Trial ID	Next event	2020e sales
Praluent	Odyssey Outcomes	18,000 pts, CV outcomes	NCT01663402	PDUFA date July 24	$1.8bn
Repatha	Fourier	27,500 pts, CV outcomes	NCT01764633	PDUFA date August 27	$2.1bn
ETC-1002	'009 study	134 pts, on top of statins	NCT02072161	'014 study readout, start of phase III	None forecast

To contact the writer of this story email Jacob Plieth in London at jacobp@epvantage.com or follow @JacobPlieth on Twitter