Evaluate Vantage

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ACC – No Repatha of glory

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Repatha is an expensive way to prevent cardiovascular events. This is the main conclusion that can be drawn from the massive Fourier trial, which found a 15% reduction in heart attacks, strokes, death and other complications of elevated cholesterol, missing investor expectations of better outcomes that would persuade payers that Amgen's injection is worth the money.

Given the scope of the Fourier trial, it seems probable that Amgen will be able to seek an expansion to its US and European label to include high-risk patients who have established cardiovascular disease. Nevertheless, Amgen shares fell 7% in early trading today as the promise of this $12,000-a-year PCSK9 antibody is likely to be limited by payers who will argue that it has a high price and modest benefit.

The knock-on effect of the Fourier trial spread to other companies working on PCSK9 modulation. Regeneron, which developed the competing Praluent, was off 5%, and development-stage groups the Medicines Company and Esperion were down 20% and 19% respectively.

The operation was a success, but…

As a scientific achievement, Repatha is a success. In the Fourier trial Repatha taken with statins lowered patients' LDL by a mean of 59%, from 92mg/dl to 30mg/dl. Compared versus statins alone, it reduced the risk of cardiovascular death, myocardial infarction, stroke, hospitalisation for unstable angina, or coronary revascularisation, a composite endpoint, by 15%; on a secondary endpoint that looked only at cardiovascular death, myocardial infarction, or stroke, the risk was cut by 20%.

As a bid to improve Repatha's commercial outlook, Fourier fell flat. The 28,000-patient trial had been powered to detect a 15% risk reduction in the secondary endpoint, and a reduction in the 15-20% range was seen as insufficient to expand the eligible patient population; by comparision, Zetia plus statins reduced the risk of myocardial infarctions by 13% and stroke by 21% (*ACC – Repatha's next challenge is expectations, March 6, 2017*).

A reduction of around 30% could have been forecast based on meta-analyses that have found that, for every 39mg/dl of LDL lowering, the risk of cardiovascular events is cut by 21%. In its pivotal trial, Repatha plus statins lowered LDL by 69m/dl.

Significantly, neither Zetia nor Repatha have an effect on cardiovascular mortality, meaning that prevention of heart attacks, strokes and other events requiring hospitalisation is driving the result. The case fatality rate was 5% in the two-year trial.

Bright spot?

Prevention of non-fatal events is certainly a bright spot of the trial, given that payers are certainly concerned with the cost of hospitalisation and procedures like coronary revascularisation.

Furthermore, the trial's chief investigator, Marc Sabatine, a cardiologist with Brigham and Women's Hospital in Boston, focused on the increased benefit seen with more exposure to Repatha – on the primary endpoint, the relative risk was reduced by 33% in the second year, an argument that Amgen could take to payers.

Whether the reduction is enough to persuade payers to allow more patients to take Repatha will be down to negotiations between Amgen and pharmacy-benefit managers like Express Scripts and CVS Caremark.

"This is very expensive stuff," said Valentin Fuster, a cardiologist and physician-in-chief at Mt Sinai Hospital in New York. "We have to be sure to identify the right population" that will benefit the most, he added.

Richard Chazal, the ACC's president and director of the heart and vascular institute at the Lee Memorial Health System in Florida, was more complimentary, pointing to the fact that all of the patients in the trial had suffered previous cardiovascular events.

"In the patient who appears to be relatively controlled but has recurrent events, all of a sudden this appears to be a pretty effective strategy," Dr Chazal said. "If I'm [otherwise] having to admit this patient once a year with

acute coronary syndrome, [Repatha] looks cost effective."

This is a debatable statement. The independent Institute for Clinical and Economic Review (ICER) calculated that for PCSK9 drugs to be cost effective their price would need to be reduced to $8,300 a year or less. That assessment could change since ICER has pledged to incorporate Fourier's findings.

There is no question that Repatha has disappointed, as its 2016 sales of $141m were less than half that forecast at its launch in 2015. The next two years were seen as an inflection point, with blockbuster numbers expected in 2018, something that now looks decidedly less likely as Amgen will need to settle for fewer patients or a lower price.

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