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More Esperion data give partners more reasons to wait

Jonathan Gardner

Assuming that the safety worries that have emerged with Esperion's cholesterol-lowering pill bempedoic acid are transitory, the Michigan-based group has a bigger concern should it secure regulatory approval: navigating the changing market for cardiovascular drugs.

With substantial price reductions now realised for the more potent PCSK9 agents Esperion could find it difficult to establish a price point that will allow it to turn a profit. Now with 52-week data hinting at an imbalance of cardiovascular deaths in patients taking bempedoic acid, the capacity of a long-term outcomes trial to show a benefit over statins ought to be questioned.

More detail, please

Esperion shares fell 30% at midday today after release of the first long-term phase III data for bempedoic acid. As this was primarily a safety study, adverse events data, and specifically liver enzyme elevations and deaths, were a focus for investors.

13 deaths were recorded among 1,487 heart disease patients taking bempedoic acid, versus two in 742 subjects in the placebo arm. Pressed further on this point, Esperion executives revealed that five of the 13 deaths in the active treatment arm and one in the placebo group were due to cardiovascular causes.

These are small numbers, to be sure, and executives were keen to emphasise the two-to-one randomisation design as helping to explain the differences, along with the fact that the deaths occurred early in the trial. Nevertheless, this is a number that the US FDA and international regulators will want to examine closely – and, without the big numbers of an outcomes trial to illuminate the meaning of these mortality numbers fully, there might be an abundance of caution.

About two thirds of the patients have rolled over into an open-label extension, which will evaluate safety at 18 months; this could shed more light on the initial safety findings.

Threading the needle

In any case the modest potency of reducing LDL cholesterol does not necessarily lend itself to a bullish case for Esperion. Chief executive Tim Mayleben has presented the bempedoic acid treatment strategy as threading the needle between cheap generic statins on the one hand and the expensive PCSK9 antibodies Repatha and Praluent on the other.

In this study, bempedoic acid patients saw their LDL levels drop by an average of 16% – from a baseline of 103.6mg/dl, mean LDL would be around 87mg/dl. Although this is modest by the standards of the PCSK9s, which lowered LDL by around 60% in this population, there are patients who might still benefit, Esperion believes. At a suggested price somewhere around $10 a day, Esperion has argued that a huge number of moderate-risk patients – those with LDL levels of 70-130mg/dl – could get to a goal of less than 70mg/dl.

However, with Sanofi having struck an exclusive deal with the large pharmacy benefit manager Express Scripts over Praluent, it seems possible that both PCSK9s might be nearing that price. Indeed, the independent evaluator Institute for Clinical and Economic Review has recommended an annual price for the PCSK9s of around $2,000 a year if used to treat patients with LDL of 70mg/dl or greater (*Bye, Repatha – price cut on Praluent wins exclusive Express Scripts deal, May 1, 2018*).

If the PCSK9s are nearing the $10-a-day mark, and bempedoic acid is launched at this price, Esperion might have a fight on its hands as physicians and patients could favour the greater LDL-lowering power of the PCSK9s. And, even at a 60% reduction in LDL the PCSK9s struggled to show that they were better at preventing heart attacks, strokes or cardiovascular events than a combination of statins and Zetia; it cannot be assumed that bempedoic acid will do better.

Mr Mayleben said the data released today would "help reinvigorate our discussions with potential partners". It would be surprising if any were more inclined to sign up bempedoic acid now.

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Clear Harmony	NCT02666664
Clear Harmony OLE	NCT03067441

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