Novartis gets surprise heart failure win as ACC data roll in

What you lose on the swings, you gain on the roundabouts. Just a few days after a US advisory committee unanimously rejected Novartis's acute heart failure project serelaxin, the data-monitoring committee for LCZ696's pivotal study has recommended early closure because it kept chronic heart failure patients alive and out of hospital longer than Vasotec.

Coming as other cardiovascular drugs are reporting data during the American College of Cardiology meeting, Novartis's announcement today is sure to create a buzz among leading specialists in the field. With detailed results from the trial expected to be disclosed at a European meeting later this year, these cardiologists will be anxiously waiting to see how LCZ696 stacks up against the Swiss group's own Diovan.

Where did that come from?

Novartis released little about the now halted Paradigm-HF trial beyond the panel's recommendation that it be stopped because of the clear efficacy advantage of LCZ696. The trial measured time to first occurrence of either cardiovascular death or a heart-failure related hospitalisation in more than 8,400 patients with chronic heart failure with reduced ejection fraction.

While serelaxin has hogged all of the attention in Novartis's cardiovascular pipeline, LCZ696 has moved quietly through its pivotal stage. Only two analysts, Bank of America-Merrill Lynch and Deutsche Bank, have included any forecast for the AT1 receptor-neprilysin (ARNI) inhibitor – the former estimating sales of $871m by 2023, the latter $500m by 2018.

But with this announcement, and in particular the release of the full dataset, more analysts will likely begin pencilling in numbers for LCZ696. Tim Anderson, with Bernstein Research, wrote this morning that it had been difficult to tell how well LCZ696 would work based only on phase II data.

This announcement reveals the pill as potentially “another blockbuster drug in the category of cardiovascular medicine that the company knows well”, Mr Anderson wrote. His only caution was the equally bullish language Novartis used in promoting serelaxin, rejected for acute heart failure in Europe and on its way to a complete response letter in the US (Serelaxin data judged incomplete as FDA panel sends it back, March 28, 2014).

But the data appeared to be enough to light a small fire under Novartis shares, which were up more than 3% to SFr74.90 in mid-afternoon trading.

Novartis's knowledge of heart failure and hypertension drugs comes from selling Diovan, at its peak a $6bn-a-year product. Like Diovan, LCZ696 blocks the action of angiotensin II, but adds a second mechanism of action in its inhibition of neprilysin, an enzyme that breaks down the vasodilatory C-type natriuretic peptide ANP.

The problem with single-action neprilysin inhibitors is that the neprilysin also breaks down angiotensin II, so blocking its action leaves more angiotensin II in circulation to act as a vasoconstrictor. If results revealed so far from Paradigm-HF are to be believed, Novartis has conquered this biological issue.

The only fault that can be raised so far is use of an ACE inhibitor, Vasotec, as a comparator arm, rather than an angiotensin II inhibitor like Diovan. Novartis could plausibly argue that it wanted to detect how LCZ696 performed against a slightly different mechanism of action; nevertheless, cardiologists will no doubt want to analyse fuller data next to see how much better than Diovan the new project is.

Upstaged

Novartis's news upstages the pharma announcements emerging from the ACC meeting in Washington, DC. Perhaps GlaxoSmithKline is happy to have its news eclipsed, as the secondary endpoints it has touted from the failed Stability trial of darapladib appear to have landed with a dull thud.

The study data were outlined at ACC and simultaneously published in the New England Journal of Medicine. The
failure to significantly protect against cardiovascular death, myocardial infarction or stroke was well known in advance (Event – Glaxo resuscitates hope in darapladib, March 21, 2014); “nominal” protection against major coronary events (hazard ratio 0.90 p=0.045) and total coronary events (HR 0.91 p=0.02) were detected.

Analysts from Bryan Garnier wrote this morning that “the ‘intriguing’ secondary endpoints are not such that a positive outcome is likely for the drug in our view”, but added that a shot on goal remains in the Solid-Timi 52 trial in patients who have undergone percutaneous coronary intervention.

Data from lipid-lowering antibodies blocking PCSK9 are also in the shadow of Novartis’s announcement. Those molecules from Amgen, Pfizer, Regeneron Pharmaceuticals/Sanofi and Roche continue to show their potent lipid-lowering power, although evidence of how they perform outside the limited settings of familial hypercholesterolaemia is not widely expected until massive outcomes trials in the broader high-cholesterol population begin to read out in 2017 and 2018.

In a five-day period marked by an FDA adcom and a major cardiovascular meeting, Novartis has managed to pull a rabbit out of its hat while GlaxoSmithKline let the audience see the cards hidden up its sleeve. The Swiss group will need to end on a flourish in a few months for it to be judged a truly star performance.

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<tr>
<th>Project</th>
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