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AHA – Two hits and several misses with Novartis's serelaxin

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There can be no doubt that Novartis's serelaxin is showing signs that it can relieve shortness of breath and maybe, just maybe, reduce mortality in acute heart failure patients. However, there are plenty of doubts about whether data from the Relax-AHF study are robust enough to warrant regulatory approval to treat these very sick patients with few medical options (*Event – Novartis heart failure data at AHA could quicken investors' pulses, September 24, 2012).*

Enthusiasm for serelaxin was tempered by the numerous missed endpoints, including alternate measures of breathlessness and mortality, and despite the fact that the data reported are late-stage it seems likely that at least one more phase III trial will be necessary. "At the end of the day I'd like to see more data," said Dr John Harold, a cardiologist at Cedars-Sinai Hospital in Los Angeles. "I'm not overwhelmed by the outcome. But we have many therapies that we weren't overwhelmed by in the beginning that over time did make a difference and became part of our armamentarium."

Breathing deeply

Shortness of breath, often described as tightness of the chest or a feeling of suffocation, is the most frequent symptom of acute heart failure events, which happen in patients with diagnosed as well as undiagnosed disease.

In particular, patients with acute episodes of diastolic heart failure are in need of medical interventions, said Dr Richard Becker, a professor at Duke University Medical Centre in North Carolina. "So far, despite much effort there has not been much that has changed the natural history of that particular type of heart failure," Dr Becker told *EP Vantage*.

The two goals met by serelaxin, also known as RLX030, in the Relax-AHF trial were patient-reported breathlessness relief measured over five days, a co-primary endpoint, and cardiovascular death by 37% after 180 days, a secondary endpoint, when compared with placebo. The second co-primary endpoint, breathlessness relief at 6, 12, and 24 hours, was not met, nor were 60-day measures of cardiovascular events, deaths, rehospitalisation or time spent out of hospital.

Serelaxin, a recombinant form of a hormone that becomes elevated during pregnancy, did reduce signs and symptoms of congestion such as oedema and breathlessness while lying down, along with intensive-care unit and hospitalisation length of stay and worsening of heart failure in the first five days of an acute event.

Dr John McMurray, a cardiology professor at the University of Glasgow, said he had no doubt that serelaxin had a benefit in relieving breathlessness based on the totality of the evidence, but struck a cautious tone on the mortality finding because the study population numbered just 1,161.

"In heart failure we have been famously misled by small numbers," said Dr McMurray. "Undoubtedly there will be some regulatory discussion about whether a single trial is sufficient."

Glimmers of hope

However, he praised the trial for selecting patients most likely to benefit and those early in the disease progression, within 16 hours of presentation. Both could lend some support to the findings, but the speed with which the patients were recruited alone may change clinical practice, said Dr Milton Packer, cardiology chairman at University of Texas Southwestern.

"As in myocardial infarction ... it could be that in acute heart failure time is of the essence," Dr Packer said. "That would be transformative in terms of our thinking process. If that mortality effect is true, this trial changes the way we do things."

Expectations have been building for the drug. *EvaluatePharma's* 2016 consensus forecast has risen 26% to

$149m since January, with the 2018 forecast now standing at $229m.

A positive mortality finding would likely drive a great deal of sales for relaxin.

“If in fact it had a mortality claim there would be a mandate to use it in every patient who came in with acutely decompensated heart failure who fulfilled the criteria,” Dr Packer said.

“To see a drug that reduces mortality is a really special thing for a cardiologist and for patients. If that mortality benefit is real, boy are we going to get excited. So the real question is whether the mortality benefit seen in this trial is a true and replicable finding.”

Study	**Trial ID**
Relax-AHF	NCT00520806

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