Serelaxin continues charmed life with breakthrough designation

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That the FDA awarded breakthrough therapy status to Novartis’s RLX030 (serelaxin), in spite of its mixed clinical results, is a sign of how urgently the regulator wants new therapies for acute heart failure. There was some thought that additional clinical trials would be necessary to tease out its benefits, particularly the impressive effect on mortality that had raised eyebrows when results were disclosed.

Optimism about the treatment is growing, with analysts nearly tripling their 2018 forecasts from the level before the phase III data were disclosed. A filing in Europe and the rather positive stance taken by US counterparts will do little to dampen enthusiasm. Still, many questions need to be answered about the hormone, not least whether the mortality benefit is real and can be replicated in a large population.

Yes, but no

The progress of serelaxin will now be aided by enhanced dialogue between Novartis and agency staff as the company prepares and submits its data package. Breakthrough status was established under legislation enacted in 2012, and the FDA has been active this year in designating new drugs as advances worthy of approval timelines faster than even those under priority review and accelerated approval; 20 of 56 requests have been granted since the start of the federal fiscal year in October (Asco – FDA charms industry with talk of faster approvals, June 3, 2013).

There is no doubt that serelaxin is showing some promising signs. The recombinant form of a hormone that becomes elevated during pregnancy reduced shortness of breath, the most frequent symptom of acute heart failure, when measured by one patient-reported method – though this result was not seen when measured by a second method (AHA – Two hits and several misses with Novartis’s serelaxin, November 7, 2012).

The bigger surprise, a reduction in all-cause mortality at 180 days, was not reinforced by measures of cardiovascular death or hospital readmission for heart and renal failure, which failed to improve in the Relax-AHF trial. These curiously conflicting findings called into question the robustness of Novartis’s data package, and even the mortality signal that was seen must be questioned because the trial had not been designed or powered to assess it.

Still, Novartis has submitted the drug to the European Medicines Agency for approval and plans a US filing very soon, with the unmet need in heart failure probably in mind. Angiotensin II antagonists are now the chief means to treat patients with acute heart failure; Novartis’s top-selling Diovan, for example, has been shown to reduce heart failure complications, but only in those patients who do not take an ACE inhibitor.

Reading the tea leaves

So it could be taken as a bit of a surprise, given the weak data, that the FDA has declared serelaxin a breakthrough. But it might be premature to read too much into the designation. After all, the breakthrough designation is only a guarantee of speedy communication with sponsors, not a fait accompli about the outcome of regulatory review.

Certainly the agency could still demand additional trials, and indeed regulators could be thinking that breakthrough status will enable Novartis to turn around a confirmatory trial faster than the five years it took to generate results from Relax-AHF – one of the goals of a breakthrough designation, as outlined by FDA officials at Asco was to minimise the size of trials or end them early when preliminary evidence of efficacy emerges.

The move also raises questions about just what regulators mean by “breakthrough” – unlike the orphan indications specified so far, heart failure affects nearly six million people in the US alone. Many of the breakthroughs awarded so far are for advances in cancer therapy, such as Pharmacyclics and Johnson & Johnson’s ibrutinib, or for orphan categories with few options, such as Vertex Pharmaceuticals’ Kalydeco and lumacaftor in cystic fibrosis – although AbbVie’s hepatitis C drugs are also included.

For a heart failure project to join these ranks raises the possibility that the FDA, which has not published
guidance on breakthrough therapies, will be flexible about what disease areas will qualify. If serelaxin lives up to the highest hopes, it might indeed fit the description of a transformative drug that deserves the label.

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