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Panel puts Fibrogen project to an almost certain death

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An FDA advisory committee refuses to overlook the potential dangers of roxadustat, Fibrogen's novel anaemia pill, leaving partner Astrazeneca with a difficult choice.

Fibrogen's roxadustat was never expected to get an easy ride in front of yesterday's FDA advisory panel, but few foresaw an almost outright rejection. US approval of the novel anaemia pill is now highly unlikely – at least not without a severely restricted label – an outcome that has repercussions for several other developers.

Firstly this means Astrazeneca, Fibrogen's US partner; after spending years and billions of dollars buffing Brilinta's benefits, the pharma giant might have little appetite for another "hearts and minds" battle. And in what cannot be a coincidence Glaxosmithkline today disclosed a successful pivotal programme of its trailing daprodustat, though there are no data in its release, and as Fibrogen has so amply demonstrated the devil is always in the detail.

That detail caused Fibrogen's stock to plunge 45% in early trade, with the market clearly considering roxadustat to be over. The company's future does not look too bright either.

Fibrogen's handling of roxadustat's clinical programme has long been criticised, with complaints of opaque and confusing presentations culminating in a staggering admission that the wrong data had been presented and initially filed with the FDA.

In a note that will be highly damaging for executives, analysts at SVB Leerink pointed out today that investors were unaware of imbalances in several new safety issues that emerged at the panel. As well as increased risk of death and thrombosis, these included rates of stent occlusion, serious infections, seizures, and metabolic and gastrointestinal adverse events.

Class effect?

These disclosures will only firm up suspicions that certain adverse events are a feature of HIF-PH inhibitors, of which roxadustat is the leading project. Akebia's disclosure of a much clearer cardiac safety signal last year with its contender vadadustat now looks even more like supportive evidence of a class effect.

The FDA last month accepted vadadustat's filing, with a decision due in March. The already dim hopes for approval must surely be lowered again in light of roxa's reception.

Thus Glaxo's daprodustat represents the last chance for the HIF-PH inhibitors to prove their potential. This rests on them being more convenient than, and at least as safe as, the standard of care – erythropoietin stimulating agents (ESAs) – in treating anaemia.

Daprodustat met its primary endpoint in all five studies that comprise the Ascend pivotal programme, Glaxo said today. The incidence of treatment-related adverse events was said to be similar in the patient groups tested across the 8,000-subject programme, while daprodustat was found to be non-inferior to an ESA in the risk of major adverse cardiovascular events.

But with no hard data in the release, and little detail beyond the topline results, it is what lies behind these claims that remains crucial.

Death knell

What is patently clear is that the FDA's cardio-renal advisory committee does not want roxadustat on the market. The panel voted 13-1 and 12-2 against approval in the two indications being sought: to treat anaemia associated with chronic kidney disease, in patients on and pre-dialysis.

The latter setting, comprising less sick patients, was always the longer shot. Panellists made it clear that another large trial should be required before approval to clear up concerns mainly of cardiac toxicity. This would likely take several years to run.

Even in dialysis-dependent patients the panel had grave doubts that roxa was any safer than ESAs. There is a sliver of hope for approval in a subset of patients who do not respond to ESAs, but this represents only around 10% of the dialysis-dependent population, according to Stifel analysts.

With criticisms of Fibrogen's statistical analyses and trial conduct also emerging, and the company's apparent admission of a damaging dose response – essentially, that giving more roxadustat causes more deaths – it is hard to see a way forward. The group proposed a dose-titration schedule, but any notion that this would be authorised without being tested in another large trial is fantasy.

As if the situation could not get any worse, readthrough to the EU must be considered. Although the CHMP recommended approval a few weeks ago, the EMA has yet to give its final authorisation.

Perhaps Glaxo will finally realise the promise of HIF-PH inhibition. But the sorry story of roxadustat's development will not make this any easier.