Evaluate Vantage

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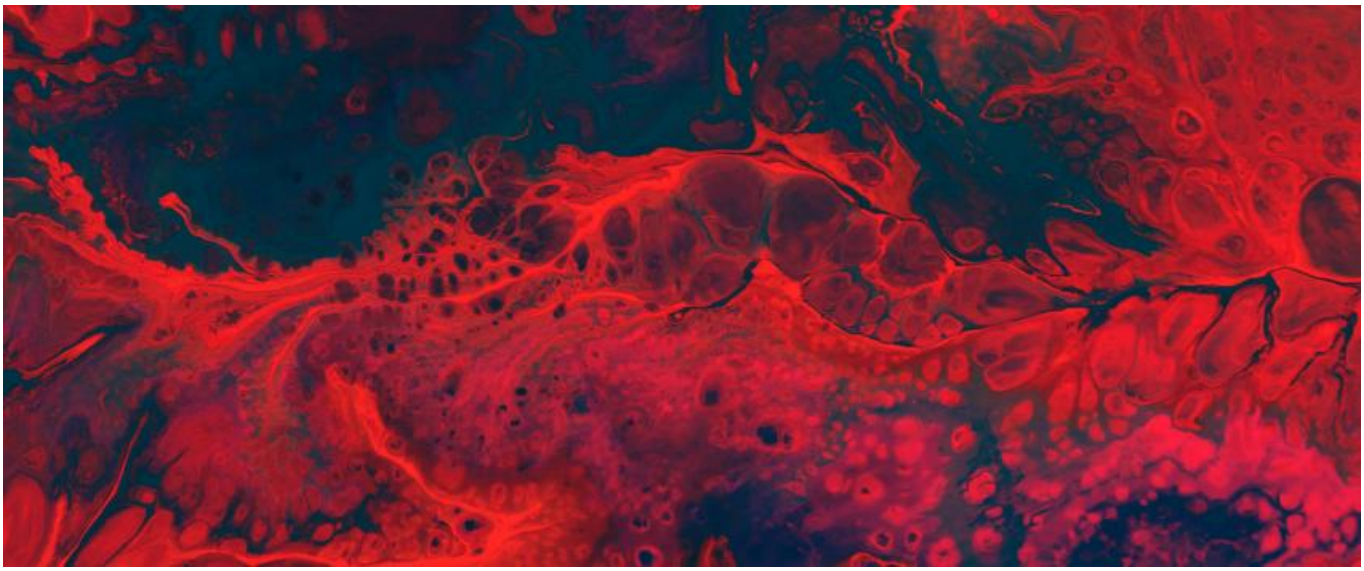
Disaster strikes for Akebia

Amy Brown



Cardiac safety threatens to derail the company’s new anaemia pill, but should rival Fibrogen be celebrating?

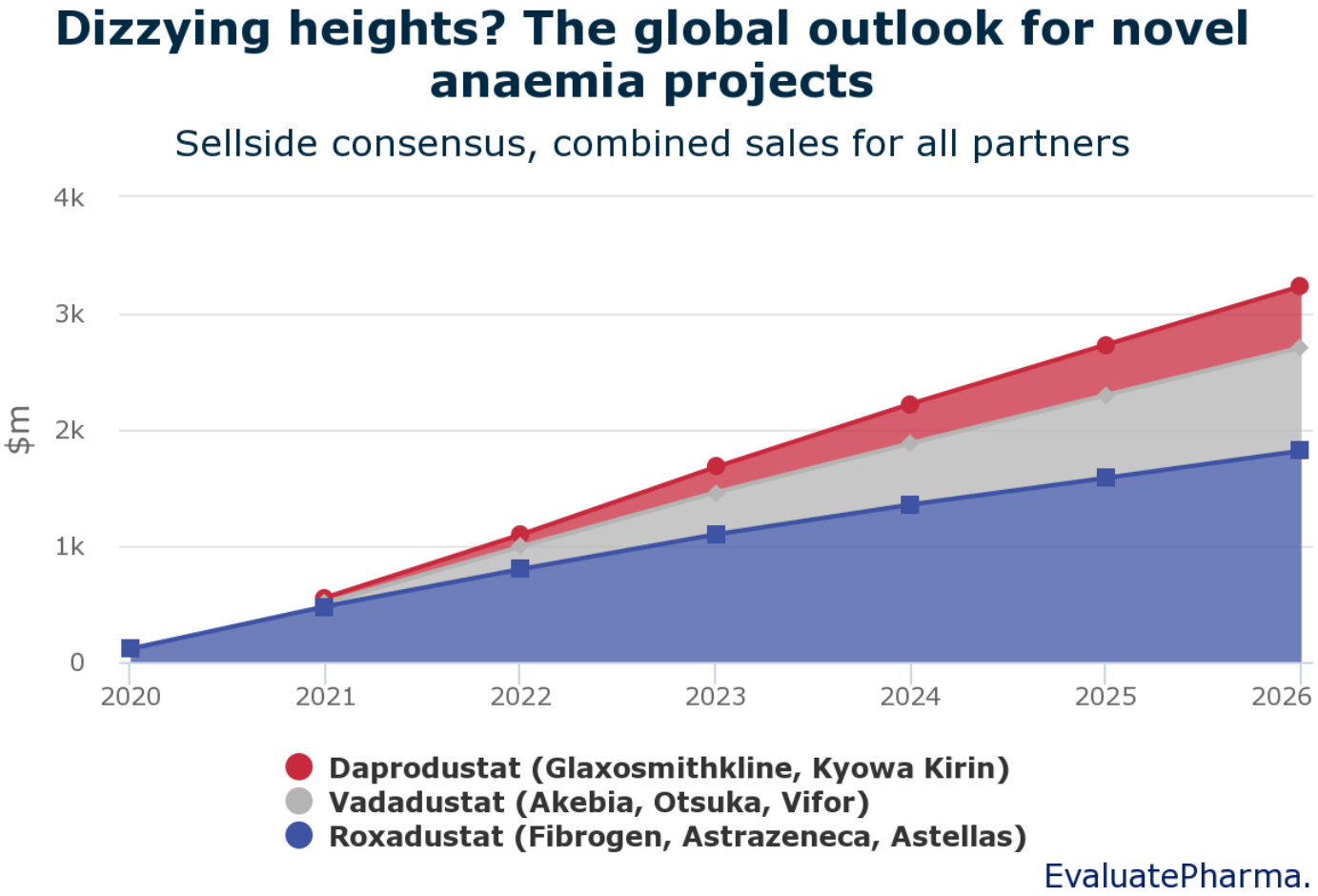
Safety concerns have long haunted Akebia’s oral anaemia project, vadadustat, and yesterday those fears materialised. The pill demonstrated worse cardiac safety than the epo agent Aranesp in two crucial chronic kidney disease studies, a finding that could wreck vadadustat’s chances of approval.

This is clearly a disaster for Akebia, which lost three-quarters of its market cap on the assumption that vadadustat is over, even if it does manage to limp onto the market. Fibrogen is already considered the leader in this field as the developer of a more advanced HIF-PH inhibitor, roxadustat, and the removal of a close rival could prove advantageous. But this company’s stock also fell yesterday, suggesting that the situation is not that simple.

True, Fibrogen shares did initially rise on the vadadustat news, and then closed down 7% as wider markets retreated. There are reasons for both caution and optimism here.

In terms of plus points, the fact that Fibrogen could have the market to itself, along with marketing partners Astellas and Astrazeneca, is certainly a big one. Glaxosmithkline also has a HIF-PH inhibitor, daprodustat, in pivotal development, but results are unlikely to emerge before 2022.

All contenders are going after two distinct markets: dialysis-dependent patients, and those yet to progress to dialysis. While epo is widely used to treat anaemia in this first group, the known cardiac risks of the class mean very few receive it in the latter setting, where patients are generally less sick.



In its pivotal programme Fibrogen demonstrated that roxadustat was non-inferior to placebo on both efficacy – mean haemoglobin change – and cardiac safety in both groups. The company is certainly not without its critics, with many concerned that roxadustat will not stand up to regulatory scrutiny. But at this point no adcom has been called ahead of a December Pdufa date, and this has been read as a positive sign.

Akebia, meanwhile, has shown vadadusat to be non-inferior to Aranesp in CKD patients on dialysis in the Inno2vate studies. This should secure approval in this indication, the company contends.

The problem lies in non-dialysis patients. In the Pro2tect trials vadadustat was again pitted against Aranesp, with the former proving non-inferior on the primary efficacy endpoint, mean change in haemoglobin. On the primary safety endpoint, time to first major adverse cardiac event, a hazard ratio of 1.17 emerged, but the upper bound of the 95% confidence interval crossed the non-inferiority margin of 1.25, extending to 1.36.

This suggests that patients in the vadadustat arm might have been at a greater risk of dying or suffering a heart attack or stroke than those taking Aranesp. Given that this margin had been prospectively agreed with the FDA it seems implausible that approval could be considered in these patients.

Approval in dialysis-dependent patients is also surely threatened; however, Akebia still has a broad label in its sights. Full data from the four-trial pivotal programme will be presented at the American Society of Nephrology's annual meeting in October, and from the "totality of the data" a path forward will emerge, executives insist.

On a conference call "regional and other patient characteristics" were hinted at, to explain the different safety findings between Pro2tect and Inno2vate. Inno2vate enrolment was skewed more to the US, Akebia executives said; it seems that blame might be laid at the feet of different standards of care in other parts of the world.

"When you see the data together you will agree we have a path forward," chief executive John Butler said. "It's not a straightforward path forward …. but we believe it supports approval in both dialysis and non-dialysis patients."

Akebia's argument thus seems somewhat contradictory, claiming that these indications are distinct, but at the same time that approval can be gained on the "totality of the data". A meeting with the FDA is planned for later this year, when regulators will have to decide whether any of this holds water.

Class effect?

The implications of all this on Fibrogen are still hard to gauge; vadadustat aside, it is far from assured that

roxadustat will get the clean, broad label the company is after. Why vadadustat would fail where roxadustat seemed to succeed also becomes a crucial question.

They are different molecules, of course, and the answer could be this simple; Fibrogen bulls have long argued that roxadustat is better designed and dosed. Trial design is another factor, with roxadustat pitted against placebo and vadadusat versus an active agent. This can also be argued in Fibrogen’s favour, as it is surely harder to demonstrate non-inferior safety against a sugar pill.

But until the FDA’s verdict on roxadustat emerges, it is impossible to rule out fears of a class effect being reflected on any label. It is understandable that some view the Pro2tect finding as increasing the chances of that outcome.