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Adcom pours fresh doubts on roxadustat's US approvability

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Just when investors thought they had seen the worst of it, the delayed Fibrogen/Astrazeneca project faces another problem.

"Our relationship with Fibrogen is fine," Astrazeneca's head of biopharmaceuticals R&D, Mene Pangalos, told *Evaluate Vantage* a month ago. Whether this holds true today, after yet another US setback to the companies' chronic kidney disease project roxadustat, is anybody's guess.

The groups' relationship was thought to have come under pressure over Fibrogen's handling of roxa's US filing, a decision on which was delayed in December by a request for more analyses. Surprising news that roxa will now face a US advisory panel, revealed last night, suggests that fears over the project's lack of safety will not easily be allayed.

Those fears had been rumbling for some time. Back in 2019 a huge analysis of roxa's seven phase III trials was meant to dismiss the risk of serious cardiovascular events, but instead was notable for what was left out; then last year cardiac toxicity hit Akebia's similarly acting vadadustat, raising the possibility of a class effect (*Disaster strikes for Akebia, September 4, 2020*).

Though the sellside rallied to Fibrogen's defence overnight, the risk to roxadustat is real, and this morning the company's stock opened down 28%. An ominous sign, as regards cardiac toxicity, is that the panel meeting will comprise the agency's cardiovascular and renal drugs advisory committee.

Why?

There is no explanation for why a last-minute decision has been made to convene an adcom, whose date has yet to be set.

Perhaps the December request for more data had raised fresh issues for the FDA, or the recent experience of Akebia with vadadustat had made it especially wary. Or maybe the agency has just decided that there is sufficient doubt around this drug class that it must have the security of expert advice before deciding on approvability.

After December's delay the FDA had set March 20 as its action date for roxa's filing, and clearly this will now be missed. The drug, an oral HIF-PH inhibitor designed to stimulate endogenous erythropoietin production, is already sold as Evrenzo in Japan and China.

It was intended to be safer than standard-of-care injected erythropoiesis-stimulating agents (ESAs). It is now abundantly clear that this idea is on shaky ground.

Black box

Assuming that roxa is approvable, the big worry remains the precise content of a US black box warning that many analysts assume is unavoidable. The adcom therefore raises the risk that the warning will include cardiovascular toxicity, something that would likely hit roxa sales in both key target populations.

Dialysis-dependent patients are typically on ESAs, which carry cardiovascular warnings, and there would be little reason to prescribe a more expensive drug like roxa if it carried similar toxicity. Meanwhile, most dialysis-independent patients are not on ESAs because of toxicity risk, so roxa would need a clean cardiovascular profile to break into this population.

At least an adcom will put to bed concerns over Fibrogen's opaque data disclosure, since the publication of briefing documents will reveal all. Though the markets had slammed the company for this opaqueness Astra refused publicly to condemn its partner's interaction with the FDA, Mr Pangalos insisting last month: "They've handled it well."

Even a best-case scenario will now not see roxa approved in the US until late this year, and according to *EvaluatePharma* consensus $2.4bn of global 2026 roxa sales is at stake. Sellside firefighting notwithstanding, the markets are right to be cautions.