

ASN 2019 preview - fears grow that roxadustat could come up short



[Madeleine Armstrong](#)



Fibrogen investors' nerves jangle as another key cardiovascular safety readout approaches for the anaemia project.

After a tough year, Fibrogen investors were probably already feeling jittery ahead of a key presentation for the group's lead project, roxadustat. And no wonder: the company has been far from transparent about roxa's cardiovascular safety, the big outstanding question as Fibrogen and its partner AstraZeneca bid for US approval.

The short seller Plainview was able to capitalise on these nerves yesterday with a report that was scathing about roxa's safety credentials and sent Fibrogen's stock down 8%. Those keeping faith with the company will hope that data being revealed on Friday at the American Society of Nephrology meeting will be more illuminating than the last update in May.

That previous analysis was light on details, with the companies not giving the actual number of major adverse cardiovascular events (MACE). These numbers will be important to gauge roxa's odds of getting the go-ahead in the US, where it is due to be filed by the end of this year for anaemia in chronic kidney disease. The project is approved in China and, more recently, Japan, where it is branded Evrenzo.

The theory is that oral HIF-PH inhibitors like roxa are safer than injected erythropoiesis-stimulating agents (ESAs), which are used to treat anaemia but are linked with thromboses and cardiovascular events.

More detail needed

The project has already shown efficacy in pivotal trials in various settings. On safety, meanwhile, Fibrogen and Astra had to show noninferiority to ESAs in dialysis-dependent patients, and noninferiority to placebo in non-dialysis patients.

On safety, so far the companies have said only that, in a pooled analysis of phase III trials, there were no clinically meaningful differences in the MACE rates between roxa and the relevant comparators, without giving figures ([Roxadustat safety analysis provokes more questions than answers, May 10, 2019](#)).

A central claim of the Plainview report is that roxa is actually less safe than ESAs. The short sellers pointed to older trials showing a higher number of events with roxa despite high discontinuation rates that should have flattered the HIF-PH inhibitor by reducing the total number of possible events.

The report argued that if this high dropout rate was repeated in phase III it would bode ill for the safety analysis. They maintained that this scenario could result in similar absolute Mace numbers with roxa versus ESAs, but a still statistically inferior result because of subjects who had dropped out and who would clearly no longer have been at risk of Mace.

Fibrogen bulls were quick to defend the company, with [one of its backers saying](#) that the high discontinuation rates were only seen in small, open-label Chinese and Japanese trials, and adding that in these studies there had been reports of doctors pushing patients to switch to ESAs.

Jefferies analysts agreed that there was nothing new in the short report, and questioned whether roxa would have got approved in China and Japan without the regulators there seeing some of the data from the major phase III trials. They also pointed to Astra's bullish comments on roxa, and the fact that the company plans to make large cash milestone payments on US filing.

Ultimately, however, only the full safety data will answer the questions still surrounding the project, and Fibrogen in particular will have to hope that the presentation on Friday will clear up any remaining doubt.

With Plainview arguing that all HIF-PH inhibitors have a safety issue, any hiccup with roxa could also be bad news for others in the space.

Top HIF-PH inhibitors in 2024

Project	Company/ies	Status	2024e sales (\$m)
Roxadustat	Astrazeneca/Fibrogen/Astellas	Approved in China, Japan; US filing due by YE 2019	1,436
Vadadustat	Akebia/Mitsubishi Tanabe/Otsuka	Filed in Japan, US phase III data due 2020	813
Daprodustat	Glaxosmithkline/Kyowa Kirin	Filed in Japan, US phase III data due 2020	400
Molidustat	Bayer	Japanese phase III trials ongoing	12

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Evaluate HQ
[44-\(0\)20-7377-0800](#)

Evaluate Americas
[+1-617-573-9450](#)

Evaluate APAC
[+81-\(0\)80-1164-4754](#)

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