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May 10, 2019

Roxadustat safety analysis provokes more questions than answers

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Fibrogen tumbles on a confusing safety update for its most advanced project.

A huge safety analysis of Fibrogen's anaemia project roxadustat was supposed to have been one of the big events of the year. In the end an update yesterday was strikingly light on details, and left investors wondering whether the company had something to hide.

Fibrogen's stock opened down 19% this morning as its backers got the jitters about roxadustat's US approval prospects. The project had already met its efficacy endpoints in pivotal trials in various settings, so the only thing that might have tripped it up now was lack of safety.

Safer?

Fibrogen is developing roxadustat for anaemia in chronic kidney disease, for which the current standard of care is injected erythropoiesis-stimulating agents (ESAs); however, these drugs are linked with thromboses and cardiovascular events.

Roxadustat is an oral HIF-PH inhibitor designed to stabilise the HIF complex and stimulate endogenous erythropoietin production, essentially mimicking the body's reaction to high altitude. It is thought that this drug class could have better cardiovascular safety than ESAs.

However, yesterday's update from Fibrogen and its US partner, Astrazeneca, left the safety profile still in question. The analysis, of seven phase III trials in around 8,300 patients, included studies in non-dialysis-dependent subjects, where the project was compared against placebo, and in dialysis-dependent patients, where it was pitted against ESAs.

For a start, the companies did not give any details on the actual number of major adverse cardiovascular events (Mace). The US FDA is interested in a strict Mace definition of death, myocardial infarction and stroke, while European regulators will be looking at Mace+, which as well as the above measures includes heart failure and unstable angina requiring hospitalisation.

In Europe, where roxadustat is partnered with Astellas, the path towards approval looks clear: on Mace+ the project showed both noninferiority to placebo in the non-dialysis-dependent setting and noninferiority to ESAs in dialysis-dependent patients. In addition, the company claimed superiority over ESAs in patients with incident dialysis, a subgroup of patients who had recently begun dialysis.

US doubts

Roxadustat's chances in the US look less clear. Fibrogen and Astra would only say that the project showed "no clinically meaningful difference" in Mace in the non-dialysis-dependent and dialysis-dependent patients versus placebo or ESAs respectively.

In the incident dialysis group the companies said there was a "trend towards benefit" on Mace. This made investors question whether roxadustat had met noninferiority on Mace, prompting this morning's selloff.

The sellside did its best to firefight today, with Leerink and Stifel saying the confusion on the Mace endpoint was at least partly down to a lack of an FDA-defined boundary for non-inferiority. However, this raises the question of why the companies had not agreed this with the agency in advance.

Leerink concluded: "Reading between the lines, it appears that the Mace event rate comparison showed similar results to the Mace+ comparison, but … the companies were unwilling to make the same declaration for the US Mace endpoint."

If this is indeed the case, yesterday's confusing press release and conference call mark a spectacular case of miscommunication from Fibrogen. Still, some investors will no doubt want to see the full data before accepting that nothing more sinister is going on.

The company expects to file roxadustat with the FDA in September or October. An advisory committee meeting looks likely – and, given the latest update, this will now be even more eagerly awaited.