Evaluate Vantage

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The dream is over for Intercept

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The company blasts the US regulator as weeks of uncertainty for its lead drug in Nash end in a complete response letter.

Six years ago the results of an investigator-sponsored study turned Intercept into a midcap company overnight, on the strength of its lead asset, obeticholic acid, in Nash. Today that dream – or its current iteration – came to a sorry end as the US FDA slapped the project with a complete response letter.

This effective refusal to approve the drug for Nash ends weeks of increasing doubt that had seen an adcom first scheduled then postponed twice. On an analyst call today Intercept slammed the agency for moving the goalposts and coming to a “premature decision, based on incomplete data”.

The filing was based on an interim readout from the pivotal Regenerate trial, and had been submitted last September. That study had shown a complex histologic endpoint was met, and positioned the drug as the first to reverse liver fibrosis in Nash (*Intercept's Nash hopes rest on Ocaliva's borderline hit, February 19, 2019*).

But concerning toxicities emerged too, including pruritus and hepatobiliary events. These did not stop obeticholic acid being approved as Ocaliva for primary biliary cholangitis, but they obviously cast a long shadow in Nash, given that this is a much broader potential indication.

Intercept’s statement on today’s setback says the FDA expressed concerns that activity based on a surrogate histopathologic endpoint might not outweigh potential risks. This is presumably a reference to the toxicities that have emerged from Ocaliva’s use.

Still, it is not entirely clear what has happened. Intercept said it was “frustrating” that there was no apparent context for the complete response letter, especially after the group had “worked in lockstep” with the agency to bring the filing to this stage.

Intercept appeared particularly annoyed that there had not been an adcom. One had initially been scheduled, but it was first delayed because of the Covid-19 pandemic, and then postponed because the FDA asked for additional data, which Intercept then submitted within a week. The June 9 action date was missed as a result.

Commitment abandoned?

“It is inexplicable why the FDA abandoned its commitment to hold an adcom,” Intercept insisted. The company said it had been awaiting instructions as to a new date for the adcom, but instead the agency issued a CRL.

The rebuff apparently asks for no additional studies, but for more data from the ongoing Regenerate trial.

Remarkably, given how Intercept attacked the FDA's actions, the company says it still hopes it can agree with the regulator on a path forward. But it admitted to analysts: "We don't have clarity on what exactly the agency is looking for. We are still digesting the impact."

Beyond the effect on Intercept, which crashed 40% this morning, the setback is yet more bad news for the Nash space in general, which has seen numerous study failures from companies including Gilead and Conatus. In May Genfit's long journey with elafibranor ended with a pivotal study failure.

However, there is one bright spot: Inventiva's lanifibranor, like elafibranor a PPAR agonist, did succeed in a mid-stage trial this month. Bulls will cling to the fact that Intercept licensed a pan-PPAR agonist, bezafibrate, from Aralez last year, and though this is not in Nash studies yet it could provide a handy pivot.

In the meantime, with Intercept now trading at its lowest point since before its 2014 explosion, Ocaliva could be in for a long delay in Nash, if it is approvable at all.