Evaluate Vantage

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Genfit’s liver disease Hail Mary approaches

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Genfit's quiet delay means it will be five years since a Nash failure before investors find out whether pressing on into phase III was worth it.

Though one Nash study after another has blown up this year, Genfit – a company with a massive retail investor following – has managed to limit its losses, even pulling off an additional listing to raise $135m on Nasdaq in March.

Now its moment of truth approaches, though not without a delay: readout of the group’s pivotal Resolve-It trial of elafibranor in Nash, earlier due in the fourth quarter, has quietly been put back by three months. This spells bad news for a binary outcome pitting bears, who point to the 2015 failure of the phase II Golden trial, against bulls, who argue that the phase III design was driven by a legitimate post-hoc analysis according to which that earlier study was in fact a success.

Whether Golden was a success probably matters little right now, and Genfit has made a strong case for looking at a different definition of its primary endpoint. But whether such a case can be proved prospectively in the pivotal setting is the big question and, even ignoring the delay, history suggests that the odds are not in Genfit’s favour.

Project	Elafibranor
Company	Genfit
Product NPV	$1.7bn
% of mkt cap	251%
Event	Interim readout of the Resolve-It study
Due	Q1 2020

In Golden neither 80mg nor 120mg of elafibranor beat placebo in terms of the primary endpoint of Nash resolution without fibrosis worsening, determined by Nash score and 12-month biopsies (*Behind the management smokescreen, Genfit study is still a fail, March 27, 2015*).

The pivotal Resolve-It trial will enrol 2,000 subjects, but it is the interim analysis of the first 1,000 that is to support US and EU filings. The 1,000 subjects having been recruited on schedule in April 2018, this interim

readout had been due by the end of 2019.

But 10 days ago Genfit quietly slipped news of the delay to the first quarter of 2020 into a statement announcing the appointment of a chief medical officer. No reasons were given, and Genfit was unavailable for comment.

Pressing on

Already Genfit's decision to press on into Resolve-it had been contentious. It was driven by three factors: that on a post-hoc reading of Golden the 120mg dose was efficacious if only the most severe Nash patients were taken into consideration; that, using a new definition of the primary endpoint post hoc, 120mg was efficacious in all-comers; and that 52 weeks was not long enough to see a fibrosis benefit.

As such, Resolve-It enrolled only subjects with a ≥4 NAS score, the severe end of Nash, and uses the new definition of Nash resolution without fibrosis worsening as well as a 72-week time frame. And sentiment around Genfit got a massive boost from a 2016 paper in Gastroenterology by Ratziu *et al* that strongly backed this new definition and the post-hoc datadredge of Golden.

According to the authors, the new definition of Nash clearance is more stringent because it emphasises hepatocyte ballooning rather than the more general disappearance of steatosis, inflammation or ballooning. Also, fibrosis worsening was newly defined as any one-stage increase, as opposed to the strict progression to bridging fibrosis or to cirrhosis specified in the Golden protocol.

This points to an alarming fact: applying the new definition to Golden's primary endpoint actually does little to flatter elafibranor's efficacy. Rather, it reduces the placebo effect that was blamed for Golden's failure, and the paper's authors readily concede this point.

Bull case

Bulls will point to the green light that Resolve-It got from its data-monitoring board in May, and to the fact that glitazone-related safety fears have not emerged.

On the other hand, elafibranor has not attracted any big-name licensing partners, and just this month Genfit's founder, Jean-François Mouney, resigned as chief executive. The delay to Resolve-it's readout, and the nature of its announcement, will have done nothing to strengthen the bull case.

So far this year has seen the Nash failures of Gilead's selonsertib and Cymabay's seladelpar – which acts similarly to elafibranor – and the highly debatable success of Intercept's Ocaliva. In the next few months the markets should know whether Genfit can buck the trend.