Evaluate Vantage

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Genfit’s predictable liver disease failure sets up a cirrhosis pivot

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Five years after failing phase II in Nash, elafibranor fails phase III in Nash; a focus on liver cirrhosis beckons.

Time and again biotech companies mistakenly push on into pivotal development armed with unconvincing phase II data. Genfit is one such company, and after yesterday reporting that its lead asset, elafibranor, crashed in the phase III Resolve-It study it has become the latest to reap its frightful harvest.

The fact that the writing had been on the wall for elafibranor as soon as its phase II Golden study failed five years ago should serve as a lesson for the investors who had credulously poured cash into Genfit, most recently $155m in a secondary Nasdaq listing. Today their investment tanked 65%.

Still, the fact that elafibranor is dead in Nash will not see the project written off. A much smaller though better-defined indication exists – primary biliary cholangitis (PBC), AKA liver cirrhosis; elafibranor has already generated phase II PBC data, and further development is to continue, Genfit told analysts yesterday.

Interestingly, a similar play is developing for Cymabay, which last November discontinued its rival Nash asset seladelpar over evidence of interface hepatitis. Today Cymabay climbed 130% after saying “an independent expert panel” had ruled out evidence of seladelpar-induced liver injury, on the basis of which it wants to resume development; if the FDA agrees PBC looks a likely indication.

Before Genfit’s failure *EvaluatePharma* sellside consensus saw elafibranor generating 2026 sales of $978m and $73m in Nash and PBC respectively. A third competitor, Intercept’s Ocaliva, is approved for PBC, and will face an FDA adcom on Nash use on June 9.

Badly wrong

How could things have gone so badly wrong for Genfit in Nash? The question is especially apt since the company’s phase II Golden trial had already failed to show a benefit for elafibranor in Nash back in 2015 (*Genfit’s liver disease Hail Mary approaches, September 19, 2019*).

The error was in reading as positive a highly questionable post-hoc analysis. This, Genfit argued, suggested a benefit in the most severe Nash subjects if a new definition of the primary endpoint was used, and an assumption was made that on this basis a positive phase III hit would result with 72 rather than 52 weeks’ treatment.

Yesterday Genfit accepted that this did not pan out, as the phase III Resolve-It trial failed at its keenly awaited interim analysis. Both the primary and key secondary endpoint drew a blank, and it is notable that despite several delays Genfit was still unable to tease out any kind of post-hoc benefit.

Genfit's two failed datasets; summary of data for 120mg elafibranor		
	Nash resolution endpoint (primary)	**Fibrosis improvement endpoint (key secondary)**
Golden (phase II trial)	Nash resolution without fibrosis worsening at 52 weeks	Reduction of histologically defined fibrosis score at 52 weeks
	21.0% vs 17.0% (p=0.280)	Failed (data not disclosed)
Resolve-It (phase III trial)	Nash resolution without fibrosis worsening at 72 weeks	≥1-point fibrosis improvement at 72 weeks
	19.2% vs 14.7% (p=0.0659)	24.5% vs 22.4% (p=0.4457)
Source: Genfit & Gastroenterology 2016.		

While the Nash resolution endpoint at least suggests a numerical benefit fibrosis improvement has drawn a complete blank.

Genfit points out that subjects who had missed a biopsy were automatically graded as non-responders. However, any hope that adjusting for this could save Resolve-It was scuppered when it admitted that the percentage of missing biopsy subjects was almost equal in the two cohorts.

Instead the company said elafibranor's efficacy was in line with expectations, but that the placebo response was "significantly higher". This is exactly the same excuse it had used five years ago for Golden's failure. Genfit also wants to take another look at biopsy data because of some possible variability.

However, management now accepts that there is no path forward for elafibranor in Nash, though it wants to consult the FDA before scrapping the Resolve-It trial entirely. With Novo Nordisk now making a concerted push into Nash, biotech looks increasingly unlikely to play a big role in this disease.