Evaluate Vantage

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Behind the management smokescreen, Genfit study is still a fail

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Management of the French company Genfit should be congratulated for the ingenuity with which they sliced and diced the data from the long-awaited Golden study of GFT505 in NASH, but the conclusion that the trial failed is inescapable.

The group's 40% fall today shows the disappointment of investors who had hoped that Genfit would repeat the trick pulled off by its rival Intercept, which had started the NASH craze in January 2014. Genfit's refusal to accept the data's clear shortcomings should give pause for thought as the group hurtles headlong into phase III.

It is still unclear what that pivotal programme will measure, though based on the Golden readout it would seem foolish to stake all on a reduction in fibrosis, an increasingly important measure (*NASH craze lives on, despite the unknowns, March 10, 2015*). Genfit yesterday said phase III would comprise up to 1,500 patients whose disease would be limited to high-risk NASH.

Failed to beat placebo

These considerations, of course, result directly from Golden's failure to beat placebo in all comers in its primary endpoint of clearance of NASH without worsening of fibrosis, determined by NASH score and baseline and 12-month biopsies.

It is telling that Genfit would not even reveal what the result was, merely stating that the design "did not enable the trial to meet directly the primary endpoint"; full data are being held back for a peer-reviewed journal. It put GFT505's failure down to a 57% response in the placebo group, and launched straight into multiple subgroup analyses.

Thus it touted a different statistical analysis to control for baseline disease severity and a large number of clinical sites (without explaining the mechanics of these adjustments) and a subgroup that excluded patients with mild NASH, whose disease resolution had driven placebo response.

On a call yesterday Genfit's chief executive, Jean-Francois Mouney, rejected the suggestion that this was data-mining, saying: "We're not slicing the data; we're just [not allowing] a placebo response to crash the whole trial."

Genfit's bullishness was remarkable, as was the fact that it backed this post-hoc, non-prespecified analysis with p values. "When we do [this] routine statistical analysis we do hit the primary endpoint," said the chief scientific officer, Dean Hum, even though this was clearly not how the protocol defined the primary endpoint.

Worse still for Genfit was Golden's miss on the secondary endpoint of reduction of histologically defined fibrosis – arguably even more important that the primary measure. "To look appropriately at fibrosis a trial should [last] at least 18 months," said Mr Mouney, insisting that the data marked a "very exciting day for Genfit".

JMP Securities said the first question was whether a fibrosis benefit would materialise over 18 months, adding that OCA had shown a 35% fibrosis improvement over 19% for placebo in the NIH's 72-week Flint trial. Baird analysts were more scathing, writing that Genfit's data announcement and conference call were "uninterpretable... Saying the results are ambiguous is being generous."

Bull

The bull case now is that Golden was a badly designed trial of a good project, and not vice versa. Investors willing to put on rose-tinted spectacles have to accept the validity of the multiple adjustments and of GFT505's positive effect on less important secondary endpoints like liver enzymes, and to bet on a fibrosis benefit emerging in a longer trial.

This is asking for a lot, and the market's clear view is that Genfit has handed Intercept a win; the Golden data were released before the US markets closed yesterday, prompting Intercept to climb 8%. Still, what the

market’s obsession with either/or scenarios ignores is that forecasts as a whole for NASH, still an ill-defined condition, might be overblown.

Look no further than Deutsche Bank’s $37bn sales potential for the NASH market. A lot can still go wrong for Intercept, especially with a $6.5bn market cap and only an investigator-sponsored trial under its belt. After all, Genfit failing does not stop Intercept from being overvalued.

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