Evaluate Vantage

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Despite a deck stacked in its favour, Tobira fails in NASH

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Tobira seemed to have given its CCR2/5 antagonist cenicriviroc the best possible chances of succeeding in a phase II NASH study, but in the event the agent has merely become another setbacк in this liver condition.

True, the company holds one strong card: cenicriviroc met an increasingly important, prospective, secondary endpoint – fibrosis improvement in just one year – that is much harder to hit than NASH (non-alcoholic steatohepatitis) improvement scores. But at best the phase II data merely point the way towards phase III design, and here Tobira's troubles begin.

This is because the group only had $52m in the bank at the end of its first quarter, and was relying on a knockout positive readout either to raise more money or strike a cenicriviroc licensing deal; the chances of either scenario now look slim.

Dim view

This morning investors took a dim view of the data, from cenicriviroc's 289-patient Centaur trial, sending Tobira down 50%. With a market cap of barely $60m a secondary equity raise looks unrealistic, while Tobira's negotiating clout with potential licensees has practically vanished.

This has not curtailed management's enthusiasm, and on a call this morning the Centaur data were billed as compelling. This is despite cenicriviroc failing to beat placebo on either the primary endpoint of NAFLD activity score, or the other secondary of steatohepatitis resolution – all the while having recruited patients at high risk of progression, maximising chances of success.

Tobira is right to call the secondary endpoint that succeeded – one-stage improvement in fibrosis with no steatohepatitis worsening – a high hurdle. Management added that it had not expected to show such a strong effect, and said Centaur included multiple endpoints because at the time it was designed there was no guidance on what might comprise an approvable measure.

Indeed, an NAFLD activity score benefit is no longer viewed as approvable, while effect on fibrosis is increasingly important. Nevertheless, a hit on a single secondary endpoint could merely be a fluke, or might be the result of uneven patient distribution between study arms, and the trick needs to be repeated in phase III.

This is the direction in which Tobira is rushing headlong; a meeting with the FDA will take place by the year end, with the aim of starting a pivotal trial in 2017. This will obviously use fibrosis improvement as primary endpoint, though Tobira would not say how many patients it would have to recruit.

2,000 patients?

The precedent is onerous: Intercept, whose obeticholic acid project started the NASH craze back in 2014, and its rival Genfit are each running pivotal NASH studies in 2,000 patients – though only Intercept measures fibrosis as primary endpoint, and that at one and a half years.

Moreover, competition in NASH is building. Tobira was the first of three groups awaiting phase II readouts this year, the others being Immuron, with IMM 124-E, and Gilead Sciences, with simtuzumab (*Therapy focus – NASH projects set for data in dog days of summer, May 3, 2016*).

There is an interesting parallel between Tobira and Genfit, which progressed its NASH agent elafibranor into phase III despite a clear phase II flop. Indeed, GFT505 failed to meet any key endpoint, and Genfit only presented phase II as positive after multiple post-hoc adjustments.

While Tobira reckons it has the first ever compound to have shown a benefit in a prospectively defined, approvable NASH endpoint, ultimately the fibrosis effect could just be a curious anomaly. True, it has done better than Genfit, but this probably only damns it with faint praise.

Selected NASH studies						
Project	**Company**	**Study**	**Primary endpoint**	**Co-primary endpoint**	**Selected secondary**	**Trial ID**
Cenicriviroc	Tobira	Centaur (ph II)	NFALD score improvement (miss)	–	48-wk fibrosis improvement (hit)	NCT02217475
Obeticholic acid	Intercept	Regenerate (ph III)	72-wk fibrosis improvement & NASH resolution	Mortality & liver outcomes	–	NCT02548351
Elafibranor	Genfit	Resolve-IT (ph III)	NASH resolution	Mortality & liver outcomes	72-wk fibrosis improvement	NCT02704403

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