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NASH craze lives on, despite the unknowns

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Just over a year ago non-alcoholic steatohepatitis turned Intercept Pharmaceuticals into a $7.5bn company in what might have been one of the worst excesses of the biotech boom. While Intercept has sold off since, recent developments show that the NASH craze is not dead yet.

With Galmed starting a phase IIb study of aramchol yesterday, and Genfit and Intercept reporting key NASH data in the coming weeks, there are numerous ways to play this market. Still, there is lack of clarity on which endpoints should be tested in phase III, and the entry of new players has made the space far more competitive than it was 12 months ago (see table below).

Nevertheless, Genfit and Intercept are moving full speed ahead towards phase III, no doubt helped by bullish sellside forecasts, such as those revealed recently by Deutsche Bank. This estimate values the global NASH market at a massive $37.1bn by 2030, with Genfit's GFT505 and Intercept's OCA sharing peak revenue of $20bn.

It is Intercept that will show its hand first, given its plans to start a phase III trial of OCA in the second quarter. A further analysis of the NIH-led Flint study, which had prompted the short-lived quadrupling of the group's share price, is to be presented at a liver disease industry colloquium on March 20-21.

Aggressive timetable

Deutsche Bank expects Genfit, for its part, to pursue an aggressive timetable to conclude its end-of-phase-II meeting over the summer and launch a phase III programme in the third quarter.

But matching or bettering OCA is only one issue for Genfit. Another is the selection of a primary endpoint for phase III, which might have to include the demonstration of a benefit in reducing fibrosis. The analysts say the group could conduct two phase III studies in parallel with different endpoints.

Genfit expects topline results from its Golden phase IIb study of GFT505, a PPAR alpha/delta agonist, at the end of March (*Upcoming events: Genfit in liver disease and Astra's new respiratory play, February 13, 2015*).

Golden has to show statistical significance in NASH, of course, but given the high expectations already baked into the stock it probably needs to show evidence of reduction of fibrosis – a key secondary endpoint. Much attention will also focus on safety.

A recent Cowen survey of NASH key opinion leaders saw only a small chance of Golden showing a statistically significant fibrosis benefit. Results, which might be presented at a late-breaker at the Easl conference in April, will be carefully compared against those of the Flint study of OCA; both trials had enrolled around 270 patients.

With Intercept stock trading back down since the first Flint readout, it is Genfit that now stands as that trial's main beneficiary – up 529% since January 2014, helped in no small part by talk that the group could be acquired.

Still, so far it is not Genfit but a relatively unknown group, Phenex, that has provided assets for acquisition – in its case by Gilead. This highlights the competition that has sprung up around the key NASH players in the wake of the Flint readout.

Selected phase II NASH projects			
Project	**Mechanism**	**Company**	**Trial ID**
Obeticholic acid	FXR agonist	Intercept	NCT01265498
GFT505	PPAR alpha & delta agonist	Genfit	NCT01694849
Aramchol	Fatty acid bile acid conjugate	Galmed	NCT02279524
Simtuzumab	Anti-LOXL2 MAb	Gilead	NCT01672879
Px-104	FXR modulator	Gilead/Phenex	–
Cenicriviroc	CCR5/CCR2 antagonist	Tobira/Takeda	NCT02217475
Emricasan	Caspase inhibitor	Conatus	NCT02077374
IMM 124-E	Metabolic disease agent	Immuron	NCT02316717
EGS21	Immunomodulator	Enzo Biochem	–

In addition to Phenex's Px-104, Gilead is also working on simtuzumab, whose phase II NASH trial could read out over the summer. Then there is Galmed, whose Aramchol yesterday began the phase IIb Arrest study; this will enrol 240 patients with NASH and concurrent obesity/insulin resistance, and US analysts expect topline data by the end of 2016.

Also yesterday, Tobira Therapeutics sold $13m of convertible debt to finance a NASH trial of cenicriviroc, a project it had earlier focused at HIV. The group had tried and failed to float in December, and instead reversed into Regado Biosciences, a zombie company that had suffered a phase III failure, the following month.

Either way, it is clear that with the biotech bull market in full swing investors are not about to forget about NASH, even if it is not, after all, Intercept that will be the sole beneficiary.

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