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Therapy focus – NASH projects set for data in dog days of summer

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Three of the industry's nine projects that are in randomised, controlled trials for non-alcoholic steatohepatitis are due to see readouts in the late summer or early autumn this year, potentially making for an eventful period in this still nascent but closely followed therapy area (see table below).

And with the NASH space only just seeing the start of its second phase III in the form of Genfit's RESOLVE-IT study of elafibranor, but with continued M&A activity for early-stage compounds, this particular area of the 2014-15 biotech bubble is likely to remain a key focus despite the recent stock market sell-off (*Gilead doesn't buy Intercept, April 5, 2016*).

The three programmes that are due to see data in the coming months are Tobira Therapeutics' cenicriviroc, Immuron's IMM 124-E and Gilead Sciences' simtuzumab. These have phase II completion dates in June, July and September respectively and might render results shortly thereafter.

Randomised, controlled phase II and III studies for NASH

Product/company	Patients	Tx period	NAS, Fibrosis stage	NCT ID	Data
Phase III					
Elafibranor/Genfit	1,800	72 wks	NAS score ≥4, fibrosis stage >1	NCT02704403	Mar 2021
Obeticholic acid/Intercept Pharma	2000	78 wks	NASH, stage 1-3 fibrosis	NCT02548351	Oct 2021
Phase II/III					
Aramchol/Galmed	240	52 wks	NAS≥4, liver fibrosis 1-3	NCT02279524	Mar 2017
Phase II					
Cenicriviroc/Tobira Therapeutics	289	52 wks	NAS≥4, liver fibrosis Stage 1-3	NCT02217475	Jun 2016
IMM 124-E/Immuron	120	24 wks	NAS>4	NCT02316717	Jul 2016
Simtuzumab/Gilead Sciences	222	96 wks	NASH, with liver fibrosis stage 3-4	NCT01672866	Sep 2016
Simtuzumab/Gilead Sciences	259	96 wks	NASH with cirrhosis, fibrosis score >5	NCT01672879	Sep 2016
BMS-986036/Bristol-Myers Squibb	105	16 wks	NASH, BMI>25	NCT02413372	Nov 2016
NGM282/NGM Biopharma	75	12 wks	NASH	NCT02443116	Dec 2016
Emricasan/Conatus Pharma	330	72 wks	NAS>4, fibrosis stage 1-3	NCT02686762	Sep 2018

Tobira's Centaur study of cenicriviroc will be important as the data will not only have to be positive but will have to support either a fundraising or partnership given the costs of moving the agent into phase III.

Leerink analysts argue that Centaur's enrolment criteria mean that it will have selected NASH patients at a higher risk of progression to cirrhosis relative to those recruited into the phase IIb studies of Intercept and Genfit's products. This should give cenicriviroc a better chance of showing a treatment effect.

DPP4 combination

Tobira has, however, given itself a more tangible advantage relative to the two lead firms in the NASH space, with its recent cross-licensing arrangement with the South Korean firm, Dong-A. This gives it the opportunity to start to develop a combination of cenicriviroc with Dong-A's DPP4 inhibitor evogliptin.

That combination approach might be able to address the underlying metabolic causation of NASH, alongside its inflammatory and fibrotic effects on the liver. Insulin resistance is known to be associated with the development of non-alcoholic fatty liver disease, of which NASH is the more severe form.

The Australian biotech Immuron has conducted a smaller and shorter duration Phase II study of IMM 124-E, with results due over the summer. This is unlikely to cause a major upset in the space, as the study uses different endpoints designed to show an effect on liver fat. Thus the programme would almost certainly require a Phase IIb to support advancing into a pivotal trial.

Meanwhile, in the early autumn Gilead should see the outcome of two phase II studies of simtuzumab, a compound that it appears to be keeping largely under wraps. Both have been conducted over long periods (92 and 96 weeks) and have recruited advanced NASH patients, either with stage 3 and 4 liver fibrosis or cirrhosis. Although phase II studies, it is possible that these may support an accelerated approval application, given the unmet need in these sicker patients.

Gilead has at least four agents in development for NASH and is presumed to have the condition in its sights for future hepatitis B or C-style domination. It is also of course the only company with the resources to conduct multiple phase III studies in the indication.

That is not the case for most of the other companies with later stage NASH programmes because of regulators' views of the data necessary to support an application. If a single pivotal study is to be used some 2,000 NASH patients will need to be treated over 72 weeks or more, as is the case for Intercept and Genfit. This would be an enormous undertaking for any biotech company and only Intercept, with some $600m cash, currently has the resources in hand to see this through to completion.

Even Genfit, with had just over €100m in cash at the end of the first quarter, has a cash runway only that extends to the interim analysis of its study, and will have to raise further funds or partner the drug to fund the study to its conclusion.

As a therapy area, NASH is unusual because it is a hypothetical and completely unmet need in pharmaceutical terms and the pipeline is still dominated by small cap biotechs. Although the wild sellside market expectations that drove the first initial enthusiasm have now tempered, it is clear that the market will be an important one in the future.

Investors and indeed corporate executives will just have to make bets on which programmes will be the most rewarding ones in meeting these needs.

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