Evaluate Vantage

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Astra first big pharma to dip toe in simmering NASH waters

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AstraZeneca looks set to become the first of the traditional big pharmas to initiate a clinical development programme in non-alcoholic steatohepatitis (NASH), the apparently common but largely undiagnosed liver condition that has at times seemed to be driving the current biotech boom.

The putative NASH space – which some sellside analysts have said could see worldwide sales of $35-40bn per year by the 2020s – has so far been dominated by two stock market darlings, Intercept Pharmaceuticals and Genfit. However, no top-tier pharma company has been active in NASH for many years, so Astra's move with AZD4076 is of more interest than would be the case of a normal candidate selection, as it suggests that the compound has met some, as yet unknown, internal hurdle.

Phase III ready

Intercept's obeticholic acid (OCA) is far and away the lead candidate for the indication, followed somewhat further behind by Genfit's GFT-505. Both compounds are ostensibly phase III-ready, but Genfit's claim is more tenuous, given that the group lacks the funds to conduct such a study, and moreover reported some decidedly chequered phase IIb data (*Behind the management smokescreen, Genfit study is still a fail, March 27, 2015*).

Intercept, which expects to finalise its protocol for phase III shortly, has just raised an incredible $367m in a secondary offering, boosting cash levels to around $800m and giving it ample resources to conduct a large phase III programme.

Both companies' stocks have been volatile, but have risen roughly fourfold in the 18 months since investor enthusiasm for NASH first took hold in the autumn of 2013.

Gilead Sciences holds a rather under-appreciated third position in the NASH space with simtuzumab, for which phase II data are due in the middle of the year. This compound tends to be overlooked by analysts, whose focus lies almost entirely on the hepatitis C franchise.

The compound's obscurity is also not helped by the fact that Gilead has guided investors to its own more cautious $6bn per year assessment of the potential market for NASH, an estimate that would be incongruous to most of the NASH stock market bulls. Six other companies have earlier development programmes in NASH.

Selected clinical-stage NASH agents			
	Project	**Company**	**Pharma class**
Phase II	Obeticholic acid	Intercept Pharmaceuticals	Farnesoid X receptor (FXR) agonist
	GFT505	GENFIT	Peroxisome proliferator activated receptor (PPAR) alpha & delta agonist
	Simtuzumab	Gilead Sciences	Anti-lysyl oxidase-like-2 (LOXL2) MAb
	Emricasan	Conatus Pharmaceuticals	Caspase inhibitor
	Cenicriviroc	Tobira Therapeutics	C-C chemokine receptor type 5/ type 2 (CCR5/CCR2) dual antagonist
	Aramchol	Galmed Pharmaceuticals	Fatty acid bile acid conjugate (FABAC)
	IMM 124-E	Immuron	Metabolic disease agent
Phase I	SHP626	Shire	Apical sodium-dependent bile acid transporter (ASBT) inhibitor
	GR-MD-02	Galectin Therapeutics	Galectin-3 inhibitor

Astra's AZD4076 is a GalNAc-conjugated anti-miR targeting microRNA-103/107. It is also the first compound Astra has selected for clinical development under a multi-product alliance covering micro-RNAs with Regulus Therapeutics. Preclinical data on AZD4076 are expected to be submitted for presentation at a scientific meeting later this year.

The company yesterday selected AZD4076 as a lead candidate to go into clinical development in NASH in patients with type 2 diabetes and pre-diabetes later this year.

Waiting in the wings

Although AZD4076 looks to become the latest asset in clinical development for NASH, there are a couple of compounds sitting in the wings that could be brought into trials quickly, if sufficient funding could be raised.

CymaBay, for example, has the PPARδ agonist MBX8025, which was licensed from J&J in 2006 and has formerly been in a phase II trial for hyperlipidaemia. Islet Sciences holds rights to remagliflozin, an SGLT2 inhibitor that has been in more extensive phase II trials.

Remigliflozin was formerly under development by GlaxoSmithKline, which discontinued it in diabetes in 2009, probably for commercial reasons, and after which it was acquired by Brighthaven Ventures and subsequently licensed to Islet. However, as a result of the compound's prior development, remogliflozin has been dosed in more than 800 people and thus could more quickly into phase II. Islet Sciences is to present preclinical data on remagliflozin activity in NASH at the upcoming EASL meeting.

The conference programme, which was released this morning, suggests that NASH investors will have new data to digest on most of these compounds in a couple of weeks' time. One abstract outside this group that has raised attention is on the potential effect of liraglutide – Novo Nordisk's Victoza – in NASH.

Given that NASH is often considered the liver manifestation of type 2 diabetes/obesity, two indications in which liraglutide has won approval, investors might be well advised to watch out for news here as well.