Evaluate Vantage

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Conatus makes a splash in NASH

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It is perhaps a sign of the excitement over non-alcoholic steatohepatitis that ambivalent phase II results could drive Conatus Pharmaceuticals' stock up 16% yesterday. The company failed to show a benefit with emricasan on portal hypertension – one of two co-primary endpoints – but highlighted improvement in a subgroup of patients with severe hypertension at baseline.

Conatus says the one-month "exploratory" trial, in patients with liver cirrhosis due to NASH or hepatitis C, sets the stage for phase IIb studies. But the company will have to do better to get a foothold in an increasingly competitive field (see table below).

The study measured hepatic venous pressure gradient (HVPG), a marker of pressure in the portal vein that the company says is accepted by the FDA as a surrogate endpoint in cirrhosis.

As the liver becomes increasingly scarred this impedes the passage of blood, which causes high pressure and can lead to problems such as varices – swollen blood vessels in the oesophagus or stomach that can rupture and bleed with potentially fatal consequences. Therefore, measuring portal hypertension is an indication of liver damage.

Biomarker improvement

Although HVPG was only significantly decreased in the most severely affected patients – those with a baseline level of 12mmHg or more – emricasan did perform on the other co-primary endpoint, with a significant reduction in cleaved cytokeratin 18 (cCK18), a biomarker specific to the drug's mechanism of action. Levels of cCK18, a marker of excessive cell death, have correlated with disease severity.

Emricasan, a first-in-class caspase inhibitor, is the only project being developed specifically to reduce apoptosis in the liver and has disease-modifying potential, according to HC Wainwright & Co analysts.

Investors seemed convinced, driving up Conatus's stock another 14% during morning trading today.

Phase II results with emricasan in portal hypertension

Patient subgroup	Mean baseline HVPG	Change from baseline HVPG	p value
Total evaluable population (n=22)	15.2mmHg	-1.1mmHg	p=0.26*
Severe portal hypertension (≥12mmHg, n=12)	20.6mmHg	-3.7mmHg	p<0.003
Less severe portal hypertension (<12mHg, n=10)	8.1mmHg	+1.9mmHg	p=0.12

**Co-primary endpoint.*

But the company still has a way to go, with two longer-term studies ongoing in liver cirrhosis and post-liver transplantation. Topline data from the former are due in the fourth quarter.

Next up is the phase IIb trial, which is likely to look at long-term outcomes in patients with cirrhosis due to various causes, said chief executive Steven Mento during a conference call to discuss the results.

The company expects to give more information on its registration strategy, including study details, by the end of the year, he added.

Dash for NASH

With NASH on the rise as obesity rates increase, it is no wonder that so many companies are clamouring to get into this space, which has been touted as the next big thing in pharma.

At the head of the NASH pack is Intercept Pharmaceuticals' obeticholic acid, which should go into phase III any time soon – the company has already given details of its 2,500 pivotal Regenerate trial.

Selected clinical-stage NASH agents			
Company	**Project**	**Status**	**Pharma class**
Intercept Pharmaceuticals	Obeticholic acid	Phase II	Farnesoid X receptor (FXR) agonist
Genfit	GFT505	Phase II	Peroxisome proliferator activated receptor (PPAR) alpha & delta agonist
Gilead Sciences	Px-104	Phase II	Farnesoid X receptor (FXR) agonist
Gilead Sciences	Simtuzumab	Phase II	Anti-lysyl oxidase-like-2 (LOXL2) MAb
Conatus Pharmaceuticals	Emricasan	Phase II	Caspase inhibitor
Tobira Therapeutics	Cenicriviroc	Phase II	C-C chemokine receptor type 5/ type 2 (CCR5/CCR2) dual antagonist
Galmed Pharmaceuticals	Aramchol	Phase II	Fatty acid bile acid conjugate (FABAC)
Immuron	IMM 124-E	Phase II	Metabolic disease agent
Galectin Therapeutics	GR-MD-02	Phase II	Galectin-3 inhibitor
Shire	SHP626	Phase I	Apical sodium-dependent bile acid transporter (ASBT) inhibitor

And the hepatitis C giant Gilead Sciences is spreading its bets in the sector. It already had a phase II agent, simtuzumab, but in January gained Phenex's farensoid X receptor agonist Px-104 (*Gilead puts small deposit down to snare NASH properties, January 07, 2015*).

Conatus is up against some stiff competition, but it believes it has a unique contender in emricasan. In future, it will need to let its data do the talking.

Phase II studies of IDN-6556	**Trial ID**
22 cirrhotic patients with portal hypertension	NCT02230683
80 patients with liver cirrhosis	NCT02230670
60 patients with post-orthotopic liver transplant for chronic HCV	NCT02138253

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