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Intercept’s safety scare ramps up Nash pressure

Madeleine Armstrong

A safety stumble for Intercept’s primary biliary cholangitis therapy Ocaliva makes its success in Nash even more important – and less likely. With questions mounting ahead of the phase III Ocaliva data readout in Nash in 2019, it is no wonder that investors are increasingly cautious about Intercept’s prospects.

Meanwhile, several rivals are nipping at its heels in primary biliary cholangitis (PBC). With different mechanisms of action, these competitors might avoid the cases of liver injury and death seen with Ocaliva (see table below).

Ocaliva’s label already warns about liver-related adverse reactions, and Intercept said the most serious events occurred in patients taking Ocaliva at a more frequent dose than recommended. Still, the safety worries, outlined in a “dear doctor” letter, sent Intercept’s share price down 14% yesterday, and the stock was off another 5% this morning.

The letter comes just over a month after a patient died in the phase II Control trial in Nash because of acute renal and liver failure. This was deemed unlikely to be related to Ocaliva, but on top of recent developments it hardly instills confidence in the project. In addition to the liver problems, Ocaliva has also been linked with LDL cholesterol elevations.

Nash bashed

One reason for extra caution is that in Nash Ocaliva is being given at higher doses – 10mg and 25mg in the pivotal Regenerate Nash study versus the 5mg or 10mg recommended in the PBC label – raising the possibility that such adverse events could be even more problematic in Nash.

If this turns out to be the case it would be a body blow to Intercept, which badly needs a result in the bigger indication. Nash is forecast to account for 65% of Ocaliva’s $1.6bn sales in 2022, according to *EvaluatePharma* sellside consensus.

However, these forecasts have come off considerably since this time last year, when Ocaliva was expected to bring in $2.7bn by 2022.

Nash seems to be losing its sparkle somewhat, with several studies seemingly having problems enrolling patients – raising doubts about whether the market is as big as forecast.

Slow enrolment has hit Genfit’s Resolve-It study of elafibranor as well as Ocaliva’s pivotal Regenerate trial; in response, Intercept tinkered with its design earlier this year, changing the definition of Nash and amending the primary endpoint analysis so the study only has to show an improvement on either Nash resolution or fibrosis improvement, rather than both (*Intercept strikes at the heart of the Nash problem, February 13, 2017*).

Still, Ocaliva remains the top prospect in Nash in 2022, according to *EvaluatePharma* sellside consensus, with expectations low for other candidates in the space.

Top five Nash products in 2022				
Project	**Company**	**Pharmacology class**	**Status**	**2022e indication sales ($m)**
Ocaliva	Intercept Pharmaceuticals	Farnesoid X receptor agonist	Phase III	1,036
GR-MD-02	Galectin Therapeutics	Galectin-3 inhibitor	Phase II	188
SHP626	Shire	Apical sodium dependent bile acid transporter inhibitor	Phase II	65
Selonsertib	Gilead Sciences	Apoptosis signal regulating kinase 1 inhibitor	Phase III	62
Aramchol	Galmed Pharmaceuticals	Fatty acid-bile acid conjugate	Phase II	32
Source: EvaluatePharma.				

As well as raising doubts about Ocaliva's prospects in Nash, the safety worries could hand an advantage to Intercept's rivals in PBC.

EvaluatePharma lists seven candidates in active phase II trials in this indication; two are farnesoid X receptor agonists like Ocaliva, so might have the same safety issues, while the rest have different mechanisms of action.

Notably, three of these PBC projects – Gilead's GS-9674, Novartis's LJN452 and Genfit's elafibranor – are also being studied in Nash.

Phase II primary biliary cholangitis candidates				
Project	**Company**	**Pharmacological class**	**Ongoing trial**	**Primary completion**
FFP104	FF Pharmaceuticals	Anti-CD40 MAb	NCT02193360	Aug 2017
GS-9674	Gilead Sciences/Phenex Pharmaceuticals	Farnesoid X receptor agonist	NCT02943447	Nov 2017
LJN452	Novartis	Farnesoid X receptor agonist	NCT02516605	Dec 2017
Elafibranor	Genfit	Peroxisome proliferator activated receptor alpha & delta agonist	NCT03124108	Apr 2018
Etrasimod	Arena Pharmaceuticals	Sphingosine-1-phosphate 1 modulator	NCT03155932*	Dec 2018
Seladelpar	Cymabay Therapeutics/Johnson & Johnson	Peroxisome proliferator activated receptor delta agonist	NCT02955602	Jul 2019
E6011	Eisai/Ajinomoto	Anti-fractalkine MAb	NCT03092765	Feb 2020
*Source: EvaluatePharma; *not yet recruiting.*				

In PBC, Cymabay Therapeutics' seladelpar and Arena Pharmaceuticals' etrasimod could be the ones to watch, according to Leerink analysts. However, while the former has shown a "meaningfully better safety profile thus far", phase II data are not due until 2019, and etrasimod has not yet begun phase II trials. Presumably elafibranor, another PPAR agonist, could have a similar profile to seladelpar.

Intercept looks like it has the PBC market to itself for a bit longer, but it is the Nash segment that it really needs to crack. The latest safety worries have made that look like a longer shot.

Study	Trial ID
Regenerate	NCT02548351

To contact the writer of this story email Madeleine Armstrong in London at madeleinea@epvantage.com or follow @ByMadeleineA on Twitter