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Intercept strikes at the heart of the Nash problem

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Changing the design of a pivotal trial rarely augurs well. But on Friday Intercept made a clever pitch that amending Ocaliva's pivotal Regenerate study in Nash would increase its chances of success as well as cutting the recruitment burden, and the sellside was sold, with upgrades pushing the stock up 5%.

True, much of what the group has done is simply a response to the low bar set by Intercept's Nash competitors. But the changes raise serious questions about whether Nash is even a disease whose treatment might realistically appear as an indication on Ocaliva's label.

Perhaps the most worrying aspect is how slowly recruitment into Regenerate had proceeded. If it has proved difficult to find sufficient patients meeting the criteria for Nash then this could contradict Intercept's claim that Nash is a growing health problem that is set to become the leading cause of liver transplants.

Nash filing

Regenerate aims to recruit 2,000 Nash patients, but a key 72-week interim analysis was to look at 1,400 of them as the basis for a Nash filing. This cohort was to have been enrolled by the middle of this year, but to stick to this schedule – and allow interim readout in 2019 – Intercept has now had to scale the interim subgroup back to just 750 patients.

It says it can do this without losing statistical power by amending the definition of Nash resolution, one of Regenerate's two key efficacy endpoints.

The new definition is more objective, it says, and does not consider accumulation of fat in the liver. The investigator-sponsored Flint trial, which had catapulted Intercept into the Nash spotlight, had used a subjective definition, with 11% of Ocaliva patients showing Nash resolution versus 3.5% for placebo recipients; using the new definition the effect in Flint would have been 20% versus 6%.

The second change involves Regenerate's co-primary endpoints: while previously Intercept was trying to demonstrate Nash resolution plus fibrosis improvement, it has now relaxed the efficacy measure to either Nash resolution or fibrosis improvement.

Clearly this lowers the perceived bar to success, but it also raises a key unknown: if Ocaliva demonstrates liver fibrosis improvement, but fails to resolve Nash, can treatment of Nash realistically be expected to appear on its label?

The question will not be answered until regulators see the results, but Intercept insists that none of its competitors has controlled data showing efficacy on both endpoints. Gilead is looking only at fibrosis in selonsertib's planned phase III trial, though this is recruiting patients with more severe fibrosis than Regenerate.

On Friday Intercept insisted that it was still confident of meeting both endpoints. Its most convincing argument about the amendment was that it now had two shots on goal instead of one, and that – if both endpoints were hit – it would still show a key advantage over competitors.

No agreement on efficacy measure in Nash					
Project	**Company**	**Study**	**Primary efficacy endpoint**	**Selected secondary**	**Trial ID**
Elafibranor	Genfit	Resolve-It (ph III)	72-wk Nash resolution	72-wk fibrosis improvement	NCT02704403
Ocaliva	Intercept	Regenerate (ph III)	72-wk Nash resolution or fibrosis improvement*	–	NCT02548351
Selonsertib	Gilead	Planned ph III	Fibrosis improvement	–	–
Aramchol	Galmed	Aramchol_005 (ph II/III)	52-wk change in the liver triglycerides	52-wk Nash resolution, fibrosis improvement	NCT02279524
Cenicriviroc	Allergan	Centaur (ph II)	NFALD score improvement (miss)	Nash resolution (miss), 48-wk fibrosis improvement (hit)**	NCT02217475
*Notes: *previously 72-wk Nash resolution and fibrosis improvement; **Allergan says FDA has indicated that ph II secondary endpoint is an acceptable registration endpoint.*					

Intercept also pointed out that its new definition of Nash resolution was in line with recent expert guidance, and was the same as that used in Genfit's phase III trial of elafibranor that looks at Nash resolution as sole primary endpoint (*Therapy focus – NASH projects set for data in dog days of summer, May 3, 2016*).

It said Regenerate remained 95% powered for both measures, and that in any case the original design was significantly overpowered with regard to detecting fibrosis improvement.

The US FDA approved Ocaliva last year for primary biliary cholangitis, an indication the sellside expects to account for 28% of its $1.8bn of forecast sales in 2022, according to *EvaluatePharma*. Meanwhile, Intercept's enterprise value stands at around $2.3bn, a figure that primary biliary cholangitis alone cannot justify.

It seems that the markets are in no mood to write off the Nash opportunity, however risky it has now become.

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