Evaluate Vantage

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Intercept's Nash hopes rest on Ocaliva's borderline hit

Jacob Plieth

Intercept’s Regenerate trial in Nash, one of the hottest clinical readouts of 2019, is technically a success, but toxicity casts a long shadow.

In showing an effect on fibrosis Intercept’s Ocaliva has met the most important endpoint in its Regenerate trial in non-alcoholic steatohepatitis – one of the sector’s most keenly awaited study readouts of 2019.

This, however, is where the good news ends. Closer reading of the results reveals a miss for Ocaliva’s lower, 10mg, dose and a worrying toxicity signal with the clearly efficacious 25mg. The stock at one point traded up 27% in the premarket but opened up 14%, a low-key reaction that might be explained by concerns that Ocaliva could lack commercial viability even if Regenerate is technically a success.

Safety concerns, of course, have long troubled Intercept. The investigator-sponsored Flint study, which turned Intercept into a Nash contender, found an increase in pruritus and LDL cholesterol, and it is likely for this reason that a 10mg Ocaliva dose was included in Regenerate in addition to the 25mg tested in Flint.

Pruritis pause

Regenerate appears to confirm the toxicity fears: of the patients given 25mg 51% reported pruritus, leading to 9% of those on this dose withdrawing from the study. The other concerning signals were hepatobiliary events and reversible increases in LDL cholesterol.

The question for Intercept is whether a therapeutic window exists for Ocaliva. It was the 25mg dose that clearly drove Ocaliva’s efficacy in terms of fibrosis improvement – one of Regenerate’s two co-primary endpoints – and was the only one to hit statistical significance according to Regenerate’s design.

Summary of Intercept's Regenerate study result			
	Ocaliva 25mg	**Ocaliva 10mg**	**Placebo**
	Stage 2 & 3 fibrosis patients		
Fibrosis improvement with no Nash worsening at 18mth	23.1%	17.6%	11.9%
p value (statistically significant?)	0.0002 (yes)	0.0446 (no)	
Nash resolution with no fibrosis worsening at 18mth	11.7%	11.2%	8.0%
p value (statistically significant?)	0.1268 (no)	0.1814 (no)	
	Stage 1, 2 & 3 fibrosis patients*		
Fibrosis improvement with no Nash worsening at 18mth	21.0%	15.7%	10.6%
Nash resolution with no fibrosis worsening at 18mth	14.9%	11.3%	7.9%
	Toxicity		
Pruritus	51%	28%	19%
LDL cholesterol increase	Peak 22.6mg/dl at 4wk		
Hepatobiliary events	3%	1%	<1%
*Note: *exploratory analysis, so of no relevance in strict statistical terms.*			

Ocaliva is already approved with a black box warning in the relatively small indication of primary biliary cholangitis (PBC), a fact that always favoured the bull thesis in Nash.

Intercept said it would pursue a dose-titration strategy in Nash that, if approved, would be similar to its approach in PBC, where patients can start on 5mg and increase to 10mg. Notably, however, the highest dose in PBC is still lower than the efficacious Nash dose.

The company seems confident that it can manage the pruritis side effect, with its chief executive, Mark Pruzanski, saying on a conference call today: “Pruritis is dose dependent and we have clear evidence in the PBC setting that titration works to ameliorate pruritis. We believe we’ve got a path forward to file 25mg.”

The company plans to submit the drug in Nash in the second half of this year in the US and Europe. Mr Pruzanski would not comment on the likelihood of an FDA advisory committee, but said this was something for which Intercept was prepared.

Nash resolution fail

Hitting one of the two Regenerate co-primary endpoints should be enough for Ocaliva to get approved in Nash, as the trial only needed to show an effect on one of the two co-primaries to be deemed a success (*Intercept’s big Nash day draws near, February 11, 2019*).

Still, the failure of either dose to show an effect on Regenerate’s second endpoint, Nash resolution, raises questions about commercial prospects in Nash.

Intercept today attempted to convince investors of the 10mg dose’s viability by pointing to analysis of “full efficacy” data from Regenerate that included 287 subjects with high-risk, stage 1 liver fibrosis. Including these post hoc does indeed flatter the 10mg dose’s performance versus placebo.

The regulator’s view on these additional subjects – termed an “exploratory cohort” – is an open question; the stage 1 liver fibrosis patients look akin to an insurance policy for Intercept. Importantly, Regenerate’s design specified that the primary efficacy analysis would involve only subjects with stage 2 and 3 fibrosis.

Mr Pruzanski would not speculate on today’s call whether Intercept might also seek approval in stage 1 fibrosis patients, but did say: “We and the FDA will be very keen to review the total population.”

Combos

The company might have a second insurance policy, too: in January it licensed the pan-PPAR agonist bezafibrate from Aralez. It might be that its long-term Nash plan now features an Ocaliva/bezafibrate

combination that could beat the monotherapy's efficacy while limiting additional toxicity.

Initially, Intercept plans to study Ocaliva/bezafibrate in PBC, and has not yet confirmed whether it will be looking at Nash. But Mr Pruzanski said today that combinations were the way forward in Nash, pointing to the heterogeneous nature of the disease. He added that the company would explore various Nash combinations, including other mechanisms.

More big readouts in Nash are due this year with Allergan's CCR type 2/5 dual antagonist cenicriviroc and Genfit's PPAR agonist elafibranor from their respective phase III trials, Aurora and Resolve-It.

Nevertheless, the PPAR approach took a knock yesterday with the phase II failure of Inventiva's lanifibranor (*Inventiva's fibrosis flop hits Nash hopes, February 19, 2019*). And another approach reached a dead end last week, with the blow-up of Gilead's selonsertib.

Today's win for Ocaliva might not have been the home run for which some Intercept bulls were hoping. But, after recent disappointments, the results should be enough to keep the Nash bubble inflated.