Evaluate Vantage

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Viking sails on favourable Nash winds

Jonathan Gardner

Positive phase II data delight investors, but Madrigal Pharmaceuticals leads in the race to market.

Nash is shaping up to be not just one big race but several smaller races among candidates with similar mechanisms of action. The competition between Madrigal Pharmaceuticals and Viking Therapeutics in the thyroid receptor agonist category got a little more interesting yesterday, with the latter producing phase II data for VK2809 that look numerically better than MGL-3196, albeit on an as-yet-unproven Nash endpoint.

The two agents will likely square off at the AASLD meeting in November, though Madrigal looks closer to approval as it has liver biopsy data in hand to permit advancing into phase III. And Viking's trial was not even in Nash but rather in the closely related non-alcoholic fatty liver disease, and was not designed to look at established Nash endpoints such as fibrosis or Nash worsening.

The primary aim of the phase II study of VK2809 was to show LDL cholesterol lowering; it also looked at liver fat as an exploratory endpoint. Non-alcoholic fatty liver disease and Nash both involve a build-up of fat in the liver, but the latter is also characterised by inflammation and liver damage.

Nevertheless, Viking investors were elated by the news of its phase II trial success, as shares rose 87%, pushing its market capitalisation over the $1bn mark.

Pictures of fat

Investors were excited by the finding that VK2809 was able to lower liver fat content by 58.1% across all doses at 12 weeks, when measured by a non-invasive technique called MRI-proton density fat fraction (MRI-PDFF), compared with a reduction of 8.9% in patients taking a placebo.

On a separate endpoint, percentage of patients achieving a liver fat reduction of at least 30%, VK2809 across all doses achieved 83.3% versus 18.2% for placebo.

Investors read this as a positive for VK2809 chances versus Madrigal's MGL-3196, which looks less effective on these particular endpoints in phase II.

Still there are reasons to be cautious due to the differences between the two studies. Madrigal's trial was larger, at 125 patients; Viking has reported data from 45 subjects in its trial.

Madrigal's trial was also specifically designed to assess liver fat changes assessed by MRI-PDFF as its primary endpoint, while secondary outcomes included the established Nash endpoints of Nash scores and fibrosis.

Madrigal versus Viking at 12 weeks				
	MGL-3196 (pooled)	**MGL-3196 placebo**	**VK2809 (pooled)**	**VK2809 placebo**
Relative change in MRI-PDFF	-36.3%	-9.6%	-58.1%	-8.9%
Significance level vs placebo	p<0.0001		p<0.01	
Percentage of patients with ≥30% liver fat reduction	60.3%	18.4%	83.3%	18.2%
Significance level vs placebo	p<0.0001		p<0.01	
Source: Company presentations.				

Viking's chief executive, Brian Lian, acknowledged that more work would likely need to be done before VK2809 was ready for phase III, especially since measuring liver fat using imaging technologies has not been endorsed by the US FDA.

“It’s known that nobody has gone into phase III without biopsy data,” he said in a call with analysts, adding that the company would like to structure the next test as a phase II/III, and acknowledging that a standalone phase IIb study might be required.

This is where Madrigal has an advantage, having reported 36-week liver biopsy data, which found that 56% of patients taking MDL-3196 achieved a reduction in NAFLD activity score of at least two points and 27% of subjects had Nash resolution.

Madrigal is designing a 900-patient phase III trial, which Raymond James analyst Steven Seedhouse believes could begin by the end of 2018 or early 2019, putting it ahead of Viking.

However, Madrigal shares tumbled 9% following the release of the Viking data.

Sizing up

Nash specialists and investors might be able to get a better side-by-side view of the two projects at the American Association for the Study of Liver Disease meeting in November, where Madrigal’s 36-week data will be featured during the presidential plenary and where Viking hopes it can get a slot for its 12-week data.

This will be a vital meeting for potential partners. The length and size of a phase III trial in Nash could stretch these companies – Intercept is enrolling more than 2,000 in its 18-month study of Ocaliva. Of four Nash assets in phase III, the only one not in the hands of a big cap firm is Genfit’s elafibranor, which will also be in a 2,000-patient trial.

Still, Genfit's presence here suggests that a small company can take on a big project on its own, and Mr Seedhouse writes that recent statements from Madrigal’s management have indicated that the group does not expect an imminent takeout offer. The company's $3.5bn market cap does not help make a case for a takeout, in any case. Depending on the full data at AASLD, Viking could represent far better value.