Evaluate Vantage

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Viking squares up to Madrigal

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It’s time for Viking, a Nash player that has climbed in tandem with one of its biotech peers, to prove itself.

In May Madrigal’s MGL-3196 wowed the markets and spurred a resurgence of interest in the liver disease Nash, and since then the company’s stock has more than doubled.

A no less spectacular doubling has been enjoyed by Viking Therapeutics, putting the stock above its April 2015 float price at last. All is now riding on the results of a phase II study of Viking’s VK2809, which like MGL-3196 is a thyroid hormone receptor beta agonist.

The double-blind trial, in 80 patients with primary hypercholesterolaemia and non-alcoholic fatty liver disease, is due to read out in the second half of 2018.

Exploratory

Interestingly, Nash is not its main focus; the primary endpoint is change in LDL-C for three active doses versus placebo. The Nash-relevant endpoint is exploratory, evaluating changes in liver fat content.

Viking says that once data are generated it expects to be in a position to move forward in either hypercholesterolaemia or Nash. Only the former is currently supported by clinical data.

The company does boast of preclinical Nash findings with VK2809, but it is only the recent surge in Nash interest that suggested this as a profitable therapy area in preference to hypercholesterolaemia, with its low margins and huge cardiovascular outcomes studies.

Viking bought the asset from Ligand Pharmaceuticals under a five-project deal in 2014 at an up-front cost of $29m, which it paid by way of an equity stake at IPO. Future milestones amount to $75m per indication, up to three indications, plus sales-based milestones and royalties.

Among supporting preclinical data in Nash are results of an eight-week study in an *in vivo* model, presented last October, showing treatment with VK2809 resulting in reductions in liver triglycerides and cholesterol, non-alcoholic fatty liver disease activity score and key measures of fibrotic activity.

Still, the bears will argue that VK2809 has never hit any Nash-relevant endpoints in humans; the bull thesis, of course, is that Madrigal’s MGL-3196 data validated the use of this pharmacology.

The Madrigal asset was squarely focused on Nash, and demonstrated significant improvements in Nash activity

score and Nash resolution versus placebo among 73 patients who underwent a liver biopsy.

Endpoints

Nash followers will be keenly aware of the importance of appropriate endpoints (*Liver disease is set for its pivotal year, August 10, 2018*).

For US approval a project likely must meet one of two surrogate endpoints: Nash resolution without fibrosis worsening or fibrosis improvement without Nash worsening. While the MGL-3196 data clearly relate to these the same cannot be said of VG2809's phase II study, and some interpretation will be needed to extrapolate from the exploratory changes in liver fat content.

A final point relates to safety, and here too Madrigal brought comfort. The main adverse event in the MGL-3196 trial was mild diarrhoea, an important finding since thyroid hormone receptor agonism has been linked to cardiotoxicity.

This plays specifically to the mechanistic strengths of MGL-3196 and VK2809: they work on the beta receptor, the major isoform present in the liver. Meanwhile the alpha receptor is mainly expressed in the heart and it is this that is related to cardiotoxicity, Viking argues.

Therefore, reading across from Madrigal to Viking, VK2809 has a good chance of showing relative safety and good efficacy against Nash in its phase II trial.

If this is the case the bigger problem could be managing investors' expectations as to the size of the market; with Viking and the sellside alike touting Nash as a billion-dollar opportunity there is plenty of room for disappointment.

Design	Trial ID
12-week study. 5mg daily, 10mg daily and 10mg every other day vs placebo	NCT02927184