Evaluate Vantage

May 17, 2023

Viking’s Voyage is not over yet

Elizabeth Cairns

A hit on one goal helps, but future Nash data will be more decisive.

After some fluctuation in Viking Therapeutics’ share price yesterday investors eventually decided that the hit on one of the two efficacy endpoints in the group’s mid-stage Nash trial was in fact a good thing, with the stock closing up 12%. But the second endpoint, Nash resolution, is more important and will not be reported for another year or so.

Until then the reductions in liver fat seen with Viking’s VK2809 look competitive, particularly with Madrigal’s resmetirom, which shares VK2809’s mechanism of thyroid hormone receptor agonism. Resmetirom posted highly impressive resolution data late last year.

Yesterday Viking said that patients in the phase 2b Voyage trial given VK2809 for three months saw reductions in liver fat – a proxy for liver health that is assessed by MRI-proton density fat fraction (MRI-PDFF) – of up to 48%, adjusted for placebo. Perhaps the best comparator here is the mid-stage MGL-3196-05 study of Madrigal’s resmetirom, which reported four years ago. This showed a placebo adjusted liver fat drop of just 23% after three months.

A necessarily imperfect cross-trial comparison is complicated further by the elaborate dosing regimen in Madrigal’s trial. Patients were given 80mg for the first month, and then remained on that dose or had their dose changed to 60mg or 100mg depending on the amount of the agent in their system.

Viking plays Madrigal: phase 2 Nash cross-trial comparison					
Drug	VK2809 (Viking)				Resmetirom (Madrigal)
Trial	Ph2b Voyage				Ph2b MGL-3196-05
Week	12				12
Dose	1mg daily	2.5mg daily	5mg QOD	10mg QOD	60-100mg daily
N	17	58	36	56	78
Pbo-adj mean relative change in liver fat by MRI-PDFF	-13%	-41%	-33%	-48%	-23%
P value vs pbo	0.082	<0.0001	<0.0001	<0.0001	<0.0001
Both trials in biopsy-confirmed Nash. QOD=every other day. Source: company release, the Lancet.					

The question is what this all means for the other of Voyage's endpoints, resolution of Nash with no worsening of fibrosis. This will be measured after a year's treatment and thus will not report until early-mid 2024.

One of the targets to beat here is also data on Madrigal's project – but from a different study. The phase 3 Maestro-Nash trial was a game-changer, with resmetirom showing placebo-adjusted rates of Nash resolution at one year of 16% and 20% with the 80 and 100mg doses, respectively.

Another benchmark was provided in March by 89Bio, whose FGF21 analogue pegozafermin allowed placebo-adjusted Nash resolution of 24% of patients with a 44mg dose, given every two weeks for six months. But this is a subcutaneous project, and thus a different prospect to the oral thyroid hormone receptor agonists.

So if VK2809 has markedly beaten resmetirom on liver fat, it is possible that it will do the same on Nash resolution – and possibly outclass 89Bio's pegozafermin too.

One project that seems highly unlikely to pose a threat is Intercept's Ocaliva. The bile acid receptor agonist is going before an FDA adcom on Friday, and with trials yielding dubious efficacy and worrying toxicity the odds are against an approval recommendation. In briefing documents for the meeting released today the agency states: "despite the modest treatment effect over placebo, FDA cannot justify [Ocaliva] use in Nash subjects with stage 2 or 3 fibrosis".

Safety

The safety of Viking's project appears excellent, at least so far, so there is no barrier to entering phase 3 at the highest doses. In Voyage a smaller proportion of VK2809 recipients had drug-related side-effects than those given placebo. This could change at the one-year point, of course, but for now things are looking good.

Safe Voyage: adverse events in Viking's Ph2b trial		
	VK2809 (all doses)	**Placebo**
N	181	65
TEAEs	82.3%	72.3%
Drug-related TEAEs	28.7%	33.8%
TEAEs leading to study discontinuation	5.0%	7.7%
Drug-related GI adverse events	8.3%	18.5%
Nausea	4.4%	7.7%
Diarrhoea	5.0%	3.1%
TEAEs=treatment emergent adverse events. Source: company communications.		

Several analysts now consider VK2809 to be best in class. SVB gives the project a 60% probability of success and forecasts peak sales of $1.2bn; this compares with 95% and $2.5bn for resmetirom. Stifel gives a 70% probability of success for VK2809, with sales peaking in 2038 at $3.6bn.

These – particularly the last – are colossal expectations. If the second readout from Voyage ends up disappointing the consequence will be little short of a Viking funeral.

More from Evaluate Vantage

Evaluate HQ
44-(0)20-7377-0800

Evaluate Americas
+1-617-573-9450

Evaluate APAC
+81-(0)80-1164-4754

© Copyright 2023 Evaluate Ltd.