Evaluate Vantage

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Madrigal changes the tune in Nash

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A smash hit in resmetirom's pivotal trial sets up an accelerated approval filing next year.

Previous late-stage failures in the liver disease Nash meant there were big doubts about Madrigal's oral thyroid hormone receptor agonist resmetirom going into its crucial phase 3 readout. But the company has prevailed where others failed, today toplining a win from the first part of the pivotal Maestro-Nash study.

Impressively, the trial succeeded on both its co-primary endpoints, Nash resolution and fibrosis, and at both doses studied. Madrigal more than tripled in value this morning on hopes that the group, which is now worth almost $4bn, can get the first Nash drug to market. That prospect should help tempt investors back into a battered biopharma sector.

The news also gave a boost to Madrigal's Nash rival Viking, whose similarly acting VK2809 is due to yield mid-stage data in the first half of 2023. That company's shares also rose 44% this morning, though its market cap is a much smaller $440m.

Madrigal intends to file for accelerated approval "as early in the second half of 2023 as possible", its chief executive, Paul Friedman, said during a conference call today.

Attention will now turn to how big this market could be: Dr Stephen Harrison of the University of Oxford, the lead investigator of Maestro-Nash, estimated that 20-25 million Americans have the disease.

If approved, resmetirom looks likely to be used in patients with non-cirrhotic Nash with moderate-to-advanced fibrosis – the population enrolled in Maestro-Nash. Even just capturing 5% of the market could lead to annual sales of $8.5bn, according to Evercore ISI analysts – an assumption they described as "conservative", that takes into account the potential impact of new obesity drugs.

Maestro-Nash flash

For now, Madrigal is basking in results described as a "best-case dataset" by SVB analysts. Today's data concerned the first, biopsy-based part of Maestro-Nash, which included assessment at baseline and again at one year. The modified intent-to-treat analysis presented today included 955 patients – biopsies were read independently by two central pathologists.

Not only did the study meet both co-primary endpoints, it did so at both doses tested, 80mg and 100mg – and showed a dose response. Placebo response rates were on the low side, but these were about in line with predictions by Evercore ISI ahead of the readout.

Best-case scenario: Maestro-Nash topline results					
Endpoint	**Resmetirom 80mg (n=316)**	**p-value**	**Resmetirom 100mg (n=321)**	**p value**	**Placebo (n=318)**
NASH resolution*	26%	<0.0001	30%	<0.0001	10%
Fibrosis improvement**	24%	0.0002	26%	<0.0001	14%
*Note: Co-primary endpoints, with fibrosis improvement added May 2022; *Ballooning 0, inflammation 0-1 with ≥2-point reduction in NAS and no worsening of fibrosis; **≥1-stage improvement in fibrosis with no worsening of NAS. Source: Company release.*					

The results surpassed expectations, which had been for a hit on the Nash resolution endpoint only. As such, resmetirom has gone one better than Intercept's Ocaliva, which in Nash only hit on the fibrosis endpoint, and only at the high dose. Despite this, Intercept has said it plans to resubmit that drug – which has previously been knocked back by the FDA in Nash – by the end of the year.

Perhaps the only thing that could trip resmetirom up now is an unexpected toxicity signal. The topline Maestro-Nash data did not raise any red flags, with nausea and diarrhoea the most common side effects – although discontinuations due to adverse events were slightly higher in the 100mg arm.

Madrigal did not give a detailed breakdown of adverse events, saying the company was still blinded to these given that the study is ongoing. Maesto-Nash also has an event-driven outcomes portion, which is due to yield data in 2026 or 2027, and is designed to support full approval.

The company's chief medical officer, Becky Taub, said that a cardiac adjudication committee, set up to look at cardiovascular events like heart attack and stroke, had not found anything untoward.

The data build on those released earlier this year from the Maestro-NAFLD-1 trial, which primarily evaluated safety but also showed promising liver fat reductions.

This year, Madrigal also started the Maestro-Nash Outcomes trial, in patients with cirrhosis, which could report in 2025.

Investors who piled into Madrigal today are perhaps hoping that, by then, resmetirom will be in the hands of a bigger player – and interest might have ticked up among those who want a piece of this large market.