Evaluate Vantage

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SFNP 2022 – Alnylam takes heart from its Onpattro follow-on

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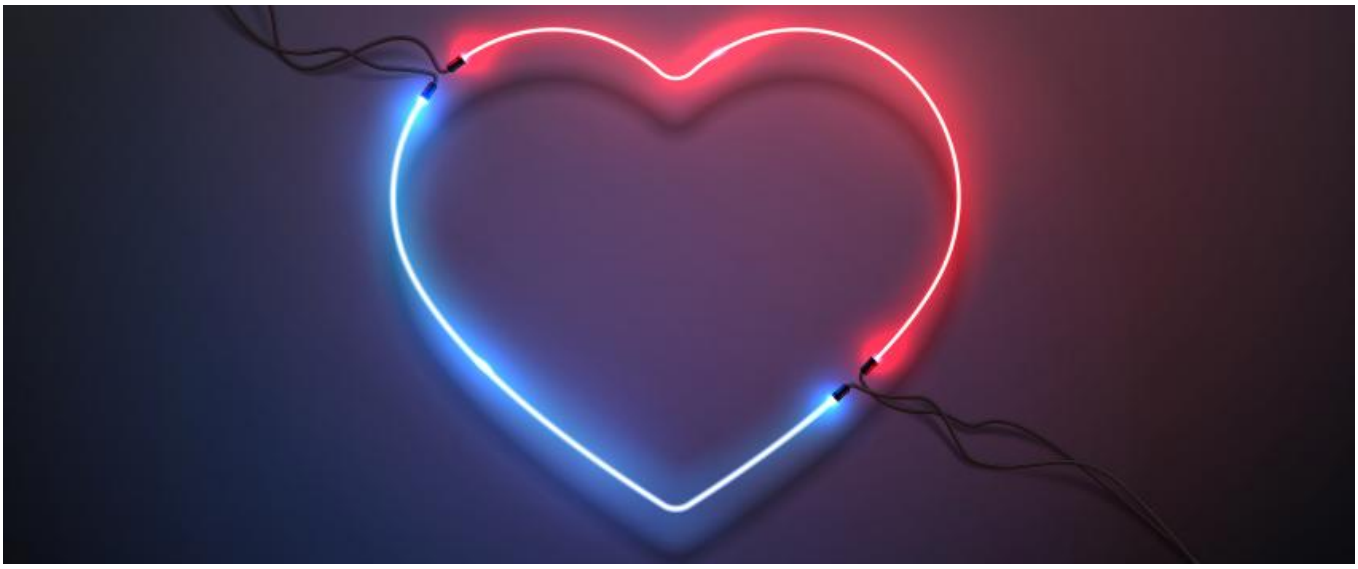

But further data do not shed much light on Onpattro's chances in Apollo-B.

Vutrisiran, Alnylam's more convenient follow-on to Onpattro, has looked approvable for a while in the polyneuropathy subtype of hereditary ATTR amyloidosis. But investors really want to know if vutrisiran – and Onpattro – can also get to market in the cardiomyopathy subtype, a bigger indication.

The biggest question is how Onpattro will perform in the Apollo-B cardiomyopathy trial, due to yield data mid-year. However, the latest results, concerning vutrisiran in polyneuropathy in the Helios-A trial, have done little to clarify things, leaving the Apollo-B readout looking as hard to call as ever.

Sentiment over Apollo-B took a hit in December with the failure of Bridgebio's Attribute-CM study of acoramidis in cardiomyopathy. Crucially, Apollo-B has the same primary endpoint as Attribute-CM: change in six-minute walk test at 12 months.

Alnylam's ATTR amyloidosis franchise			
Project/product	**Description**	**2026e sales ($m)**	**Status**
Onpattro	Intravenous RNAi, dosed every 3wks	742	Approved for polyneuropathy of hereditary ATTR amyloidosis in 2018, backed by Apollo; Apollo-B in cardiomyopathy (wild type & hereditary) to read out mid-2022
Vutrisiran	Subcutaneous RNAi, dosed every 3mo (twice-yearly dosing also being tested)	1,813	Pdufa April 14, 2022 in polyneuropathy of hereditary ATTR amyloidosis, backed by Helios-A; Helios-B in cardiomyopathy (wild type & hereditary) to read out early 2024
ALN-TTRsc04	Subcutaneous RNAi, potential annual dosing & greater potency	-	Preclinical; IND due 2022
Source: Evaluate Pharma and company presentations.			

The latest readout concerned vutrisiran, Alnylam's subcutaneous follow-on to Onpattro. 18-month data from the Helios-A trial in hereditary ATTR amyloidosis with polyneuropathy were presented at the Société Francophone du Nerf Périphérique meeting.

Various measures showed greater separation between vutrisiran and placebo at 18 months compared with the nine-month results from the same study that featured at the American Academy of Neurology meeting last April (*AAN 2021 – Helios backs Alnylam's sunny forecasts, April 20, 2021*).

As previously disclosed, Alnylam used a historical placebo arm from the Apollo study of Onpattro. Apollo had supported that product's approval in polyneuropathy.

However, on the modified Neuropathy Impairment Score (mNIS+7), vutrisiran at 18 months looked less impressive than Onpattro, which had shown a six-point decrease at the same time point in Apollo. Stifel analysts noted that Helios-A patients had lower disease burden at baseline, making cross-trial comparisons even more difficult than usual.

Maturing data from Helios-A				
	9mth data with vutrisiran	**External placebo at 9mth**	**18mth data with vutrisiran**	**External placebo at 18mth**
mNIS+7*	-2.2	14.8	-0.5	28.1
Norfolk QOL	-3.3	13.0	-1.2	19.9
10MWT (m/sec)	-0.001	-0.133	-0.024	-0.264
*Note: decrease in mNIS+7 and Norfolk QOL represent improvement; increase in 10MWT represents improvement. *mNIS+7 at 9mth is primary endpoint. Source: company presentation.*				

Helios-A also looked at several exploratory cardiac endpoints. At 18 months the adjusted geometric fold change ratio for NT-proBNP, a measure of cardiac stress, was 0.94 with vutrisiran versus 1.96 with placebo. High levels of NT-proBNP indicate heart failure.

Alnylam also claimed "encouraging trends" on echocardiographic parameters, and highlighted a reduction in cardiac uptake of technetium in a subset of vutrisiran-treated patients; the latter suggests a reduction in amyloid burden in the heart. However, this endpoint was not tested in Apollo, so there is no placebo group for comparison.

Less severe

Optimists will see all this as positive for the Apollo-B readout, but in reality things are still far from clear.

One theory put forward to explain Bridgebio's failure with acoramidis is that Attribute-CM enrolled milder patients than the successful Attr-act study of Pfizer's Vyndaqel, the only product approved for cardiomyopathy

(*Novo bets against Crispr for amyloidosis, July 13, 2021*).

It is thought that this made it hard to show separation between acoramidis and placebo patients, who declined less dramatically than expected.

There are also doubts about the six-minute walk test's utility as an endpoint, amid suggestions that a training effect might have occurred in Bridgebio's trial. To try and combat this, Alnylam is minimising the number of screening and baseline assessments, execs said at the recent JP Morgan meeting.

Still, they did not provide a detailed breakdown of the severity of disease in Apollo-B by New York Heart Association class, something analysts had been hoping to see. The trial has enrolled NYHA classes I to III, representing a range from no symptoms to marked limitation in activity.

Alnylam's stock dipped 1% on Friday and is down another 5% this morning. Expect uncertainty to continue until Apollo-B reads out.