Evaluate Vantage

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Alnylam shoots for the heart

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With readout of Apollo-B approaching, can Onpattro succeed where Bridgebio's acoramidis failed?

Alnylam is living the biotech dream, with not one but three products approved so far. However, for the group to move into the big league it needs to get a result in the Apollo-B trial of Onpattro in the cardiomyopathy subtype of ATTR amyloidosis.

Data are due mid-year, and investors are skittish after the failure of Bridgebio's rival cardiomyopathy project acoramidis in the Attribute-CM study. This had the same primary endpoint as Apollo-B: change in six-minute walk test at 12 months.

Project	Onpattro
Company	Alnylam
Market cap	$16.3bn
Product NPV	$2bn
% of market cap	12%
Event type	Topline results from ph3 Apollo-B (NCT03997383)
Indication	ATTR amyloidosis with cardiomyopathy
Date	Mid-2022

Apollo-B's outcome looks hard to call, and this is neatly illustrated by disagreement among the sellside. Stifel analysts are still confident of the trial's chances, while Berenberg gives it a 30% probability of success.

All will become clear soon, and the results will be important not just for Onpattro but also for Alnylam's more convenient follow-on RNAi project vutrisiran. The latter is also in a cardiomyopathy study, Helios-B, which is set to read out in 2024; however, that trial primarily looks at mortality and cardiovascular events at 30 months.

Polyneuropathy vs cardiomyopathy

ATTR amyloidosis is a progressive disease caused by the build-up of amyloid deposits in organs and tissues. The most common areas are around the peripheral nerves and heart, so the disorder is broadly classified into polyneuropathy and cardiomyopathy subtypes. Although there can be overlap between these subtypes, cardiomyopathy is thought to affect more than 300,000 patients worldwide, versus just 50,000 with polyneuropathy.

This explains why the Apollo-B readout is so important to Alnylam; Onpattro is already approved for the polyneuropathy subtype.

The big question for Alnlyam is not so much how Onpattro-treated patients will perform, but how those in the placebo arm will do. In Bridgebio's failed Attribute-CM trial, acoramidis-treated patients had a 9m decline in 6MWT distance, well within the group's target of 20m or lower. However, placebo patients did much better than expected, only declining 7m.

This came in sharp contrast to the Attr-act trial of Pfizer's oral amyloidosis drug Vyndaqel, conducted several years ago, which found a 25m decline in 6MWT distance at 12 months, versus a 56m drop with placebo.

Alnylam therefore needs the placebo group in Apollo-B to be more "Attr-act-like" than "Attribute-CM-like".

Should Apollo's placebo arm look comparable to Attribute-CM's, Berenberg analysts calculate that Onpattro will need to show an improvement of at least 20m on 6MWT – a big ask. Meanwhile, if the placebo effect falls between that seen in Attr-act and Attribute-CM – something Stifel sees as likely – Onpattro would need to show "near stabilisation" on 6MWT, equivalent to a 4m decline, those analysts reckon.

New normal?

So, was the placebo performance in Attribute-CM a blip, or does it represent a "new normal"?

There are various theories for Bridgebio's failure, including suggestions that Attribute-CM enrolled patients with less severe disease at baseline than the Attr-act study of Vyndaqel. It is thought that increasing awareness of amyloidosis is leading to earlier diagnosis, so patients are healthier at baseline – and healthier patients tend to have a slower decline, making it hard to show separation between therapy and placebo.

Notably, compared with Pfizer's Attr-act trial, Bridgebio's study enrolled more wild-type patients, who progress more slowly than those with hereditary disease, and more patients with less severe disease based on New York Heart Association class.

Berenberg sees this as the main reason for Attribute-CM's failure. If true, this would bode ill for Alnylam, as Apollo-B recruitment took place during a similar timeframe as the Bridgebio study.

However, the bullish Stifel analysts brushed off this explanation, saying they did not believe Attribute-CM's population to be much healthier than Attr-act's.

An alternative theory is that a "training effect" might have occurred in Attribute-CM. Alnylam hopes to minimise the potential for this confounding Apollo-B by only conducting one 6MWT eligibility assessment, versus Bridgebio's two to three.

It should soon become apparent who is right, and whether Onpattro has a future in cardiomyopathy.