Evaluate Vantage

August 14, 2017

Event – Alnylam shoots for the moon with Apollo

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With expectations sky high ahead of the Apollo readout, Alnylam's amyloidosis project patisiran has a lot to live up to – and any hint of disappointment could send the group's stock crashing back down to earth.

Investors will be keeping an eye on safety after last year's discontinuation of another Alnylam RNA interference candidate, revusiran, after several deaths. The company maintains that its technology was not to blame but, with patisiran and revusiran closely related, it seems unwise to write off the possibility of a safety signal, as many seem to have done.

Of course, patisiran will have to show efficacy too, and here confidence has rocketed after the pivotal trial success of Ionis's rival project inotersen, which has the same mechanism of action. Meanwhile, adverse events and a patient death with inotersen have raised hopes that patisiran will become the treatment of choice (*Investors scent blood after death in Ionis trial, May 15, 2017*).

Project	Patisiran
Company	Alnylam Pharmaceuticals
Product NPV	$2.67bn
% of market cap	37%
Event	Apollo trial results
Date	Mid to late September

While many believe that patisiran could be more potent and less toxic than inotersen, there are reasons to be cautious: Alnylam's asset is delivered via a three-hour infusion, versus inotersen's subcutaneous injection. Patisiran will need to show a clear win on efficacy to outweigh convenience disadvantage.

Lift off

Nevertheless, Alnylam's stock has surged 27% since results of inotersen's Neuro-TTR trial were reported. And the group got another boost on Friday after Ionis's partner, Glaxosmithkline, decided to opt out of development (*Ionis absorbs Glaxo rare disease cull, August 11, 2017*).

Ionis is looking for another partner but Alnylam, which had already been forecast to dominate the familial amyloid polyneuropathy market, is expected to press home its advantage with Glaxo out of the picture.

That is if Apollo is a success. The study's primary endpoint is change in the modified neuropathy impairment score +7 (mNIS+7), versus placebo, at 18 months. Secondary endpoints include changes in quality of life, motor function and autonomic function.

Inotersen's pivotal trial also had mNIS+7 as a co-primary endpoint, along with the Norfolk quality of life-diabetic neuropathy measure. Ionis has not reported detailed results, only saying that both endpoints reached statistical significance with p values of <0.0001 and 0.0006 respectively.

More data will be needed to see how the agents stack up against each other, but if Apollo is positive Alnylam plans to file for US approval by the end of the year, with an application in Europe expected soon afterwards.

As well as addressing the 10,000 familial amyloid polyneuropathy patients, patisiran could get approved in the 25,000 to 30,000-patient strong mixed cardiomyopathy/neuropathy population, Credit Suisse analysts believe, depending on how it performs on cardiac measures in Apollo.

Safety first

Alnylam's rehabilitation has been remarkable – the group's stock is now trading above where it was last October, when it scrapped revusiran after an imbalance in cardiovascular deaths in the Endeavour trial

(*Alnylam failure puts RNAi under the spotlight again, October 6, 2016*).

Investors have seemed keen to overlook any shadow these events might have cast on patisiran. The two projects target some overlapping RNA sequences, but patisiran is given at a lower dose, so Alnylam believes that it could avoid the same safety issues.

In any case, the group is adamant that revusiran was not to blame for the deaths, recently hosting a roundtable during which it presented cardiac marker data from Endeavour. According to the company, changes in these markers were similar between the active and placebo arms, which Alnylam argued showed that revusiran had not driven cardiotoxicity; however, this remains difficult to prove either way.

Alnylam's pipeline		
Project	**Indication**	**Net present value ($m)**
Phase III		
Patisiran*	Amyloidosis	2,336
Fitusiran	Haemophilia A/B	1,189
Phase II		
Givosiran	Porphyria	326
Inclisiran**	Cardiovascular disease/ hyperlipidaemia	287
ALN-CC5	Paroxysmal nocturnal haemoglobinuria	35
ALN-HBV	Hepatitis B	26
ALN-GO1	Kidney stones	5
Phase I		
ALN -TTRsc02	Amyloidosis	14
*Source: EvaluatePharma; *partnered with Sanofi; **licensed to The Medicines Company.*		

With a question mark still hanging over patisiran's safety, a lot is riding on the Apollo readout. The company has other projects in development but the amyloidosis candidate is by far its most valuable asset.

Success in Apollo should help validate Alnylam's RNAi platform but, with the technology still largely untested, anything less than a slam dunk could raise doubts about the company's entire pipeline.

Study	**Trial ID**
Apollo	NCT01960348

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