

## Therapy focus - Pfizer blows hereditary amyloidosis fight open



[Madeleine Armstrong](#)

Hereditary amyloidosis had been looking like a two-horse race between Alnylam and Ionis until Pfizer's surprise win last week with its candidate tafamidis. The sellside had put Alnylam's candidate patisiran way out in front, but fears that a big pharma rival could change the picture sent Alnylam's stock down 23%.

Alnylam is particularly vulnerable because of high expectations for its next-generation amyloidosis project, ALN-TTRsc02, as well as its heavy reliance on patisiran (see tables below). Ionis got off relatively lightly with a 9% share price fall, probably because it has long been seen as an amyloidosis also-ran.

Patisiran and Ionis's inotersen are both expected to get US approval this year, and analysts expect them eventually to capture 75% and 25% of the market respectively.

Alnylam's pipeline				
Project	Indication	Mechanism of action	2022e sales (\$m)	NPV (\$m)
<b>Filed</b>				
Patisiran	Hereditary ATTR amyloidosis	TTR RNAi therapeutic	959	4,284
<b>Phase III</b>				
Givosiran	Acute hepatic porphyrias	Aminolevulinic acid synthase RNAi therapeutic	237	905
Fitusiran*	Haemophilia	Thrombin III RNAi therapeutic	10	412
Inclisiran**	Hypercholesterolaemia	PCSK9 inhibitor	-	536
<b>Phase II</b>				
Cemdisiran	Complement-mediated diseases	CCR5 RNAi therapeutic	16	38
Lumasiran	Primary hyperoxaluria type 1	Glycolate oxidase inhibitor	7	20
<b>Phase I</b>				
ALN-TTRsc02	Hereditary ATTR amyloidosis	TTR RNAi therapeutic	341	414

\*Licensed to Sanofi, \*\*Licensed to The Medicines Company. Source: EvaluatePharma, company websites.

One question still hanging over patisiran is whether it will be approved in the broad amyloidosis population, including patients with cardiac involvement. Traditionally, amyloidosis has been categorised depending on where the damage is most severe - polyneuropathy for those with nervous system damage or cardiomyopathy for those with heart disease.

The pivotal trial of patisiran, Apollo, only enrolled patients with polyneuropathy, but Alnylam has pointed out that 56% of subjects enrolled also had symptoms of cardiac involvement. The company maintains that amyloidosis is one disease; its chief operating officer, Yvonne Greenstreet, has previously told *EP Vantage* that patisiran should secure a broad label ([Interview - Alnylam needs to get the price right for patisiran](#), February

12, 2018).

The emergence of Pfizer's tafamidis has thrown this into doubt. Last week's successful phase III trial, ATTR-ACT, was specifically in cardiomyopathy, which makes up the larger proportion of the market.

Furthermore, the study found a benefit with tafamidis on mortality and cardiovascular events. While Pfizer has not released detailed data, this should give its project an edge over both patisiran and inotersen, which have only shown improvements in surrogate markers of cardiac function.

Evercore ISI analyst Umer Raffat noted that, before tafamidis, no project had succeeded in this indication. The unmet need might previously have worked in Alnylam's favour and made the FDA more sympathetic to the company's request for a broad label for patisiran – but with the tafamidis on the horizon this could now be less likely.

Even if patisiran is approved in cardiomyopathy, the emergence of a new rival has evidently made investors less confident about long-term prospects for Alnylam's project. Tafamidis, an oral transthyretin stabiliser, promises greater convenience than patisiran, which is given intravenously. Pfizer's candidate, a small molecule, might also be cheaper.

Interestingly, tafamidis was knocked back by the FDA in polyneuropathy in 2012 after a phase III failure, but is marketed in this indication in Europe as Vyndaqel. It is unclear how the project managed to pull off a win in the tougher cardiomyopathy indication considering its inauspicious past.

### **Next generation**

Alnylam and Ionis will now have to adjust to a new reality which, as well as hurting patisiran and inotersen, could also scupper their next-generation candidates.

Alnylam plans to take its once-quarterly subcutaneous project, ALN-TTRsc02, into phase III by the end of the year. Timing is now everything – if Alnylam is planning a specific cardiomyopathy trial it will need to get that fully enrolled before tafamidis is approved, as patients would be reluctant to take the chance of receiving placebo if a therapy is already available.

Meanwhile, AKCEA-TTR-LRx, being developed by Ionis and its subsidiary Akcea, will not even enter the clinic until later this year, so could face an even tougher path to market with tafamidis on the scene.

With the exception of tafamidis little has changed in the late-stage hereditary amyloidosis pipeline since *EP Vantage* last looked at the space nearly two years ago ([Therapy focus – Amyloidosis pipeline still looks to Alnylam for answers, June 23, 2016](#)).

## Hereditary amyloidosis projects in active clinical development

Project	Company	Mechanism of action	Route of admin	Trial	2022e sales (\$m)
<b>Filed</b>					
Patisiran	Anylam Pharmaceuticals	TTR RNAi therapeutic	IV	Apollo, NCT01960348	959
Inotersen	Ionis Pharmaceuticals	TTR antisense	SC	Neuro-TTR, NCT01737398	442
<b>Phase III</b>					
Tafamidis*	Pfizer	TTR stabiliser	Oral	ATTR-ACT, NCT01994889	186
<b>Phase II</b>					
GSK2315698	Glaxosmithkline	Serum amyloid P component depleter	IV & SC	NCT03044353	-
GSK2398852	Glaxosmithkline	Anti-serum amyloid P component MAb	IV	NCT03044353	-
AG10	Bridgebio Pharma	TTR stabiliser	Oral	NCT03458130	-
<b>Phase I</b>					
ALN-TTRsc02	Anylam Pharmaceuticals	TTR RNAi therapeutic	SC	NCT02797847	341
PRX004	Prothena	Beta amyloid A4 protein antibody	IV	NCT03336580	-

\*Approved in Europe as Vyndaqel for familial amyloid polyneuropathy. Source: EvaluatePharma.

Two new projects have entered the fray in form of Bridgebio's AG10 and Prothena's PRX004; however, the latest studies of these agents have yet to start recruiting.

Others seem to have fallen away, including Corino Therapeutics and Som Biotech's SOM0226, which completed a phase I/II study in 2015 but does not appear to have progressed since.

The analysis above does not include projects being developed solely for light-chain amyloidosis - also known as AL amyloidosis - which stems from faulty plasma cells and in which several multiple myeloma drugs are currently being studied ([Ash therapy focus - the other amyloidosis gets its day in the sun, December 7, 2017](#)).

A combination of two Glaxosmithkline agents is being evaluated in both TTR cardiomyopathy and AL amyloidosis. This dual approach involves a serum amyloid P (SAP) depleter to decrease circulating SAP, and an anti-SAP monoclonal antibody designed to reach residual SAP in amyloid deposits.

A phase I trial of the combo had a primary completion date of October 2017, according to Clinicaltrials.gov; at the time of publishing, Glaxo had not responded to an enquiry about when data might be available.

The sellside has so far not ascribed much value to any of these projects, and even expectations for tafamidis were previously low. Surely this is about to change.

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