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Therapy focus – Amyloidosis pipeline still looks to Alnylam for answers

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The failure of Bellus Health's phase III amyloidosis trial reaffirms Alnylam's position in the race to develop a treatment for this rare disease. Sitting alongside it are phase III candidates from Prothena and Takeda, and all should start generating data within the next two years.

Further down the pipeline timings are less clear, but both large and small companies are looking into the space, with GlaxoSmithKline boasting three assets in early development (see table). With the only marketed product Pfizer's Vyndaqel still not available in the US, there is everything to play for.

Setbacks

Bellus's Kiacta failed to slow renal function decline in patients with AA amyloidosis, the primary endpoint of its phase III trial. AA amyloidosis is often caused by chronic infection or inflammatory disease that leads to amyloid accumulation in the kidneys, liver and spleen.

The company, which has just C$9m ($7m) in cash and no marketed products, saw its stock plummet by 86% this week on the news. Kiacta has had a tortuous development path, and it looks like little can now be done to salvage it *(Therapeutic focus – Amyloidosis options emerging from Pfizer, Alnylam, May 31, 2012).*

Another recent disappointment was Ionis Pharmaceutical's IONIS-TTRRx, which was hit with safety issues in a trial in familial amyloid polyneuropathy (FAP), a form of amyloidosis that affects nerve tissue. Cases of severe thrombocytopenia were reported *(Ionis safety blow boosts Alnylam, May 27, 2016).*

Subsequently a study in familial amyloid cardiomyopathy (FAC; accumulation in the heart) was put on hold until more data from the neuro trial become available. Results are expected in the first half of next year, and are key for partner Glaxo to make a decision on an ongoing relationship.

Remaining ahead

The setbacks have boosted Alnylam, whose two phase III assets, patisiran and revusiran, are being tested in FAP and FAC respectively.

Patisiran's pivotal study, Apollo, is due to read out by the middle of next year, with a primary endpoint of change in neuropathy impairment score. Positive results were previously seen in a small open-label phase II trial (*Study read-across and biotech bull market help Alnylam climb, October 14, 2014).*

Meanwhile, revusiran's Endeavour study is enrolling, and results are due in mid-2018. Primary endpoints include the six-minute walk test and differences in serum transthyretin levels.

Patisiran and revusiran are RNAi therapeutics that knock down wild-type and mutated forms of transthyretin, a protein that when misfolded leads to amyloid accumulation in amyloidosis. Ionis's IONIS-TTRRx is an antisense project designed to reduce the production of transthyretin.

Alnylam and its partner Sanofi have not seen thrombocytopenia in trials, suggesting that this could be an antisense-related effect. If the safety issues suffered by Ionis can be avoided patisiran and revusiran could sell $690m and $794m in 2022, according to *EvaluatePharma* sellside consensus.

Alnylam also has ALN-TTRsc02, which recently entered phase I as a once-quarterly treatment.

Selected amyloidosis pipeline					
Status	**Project**	**Company**	**Pharmacology class**	**Type of amyloidosis**	**Trial ID**
Phase III	Patisiran	Sanofi/Alnylam	Transthyretin RNAi therapeutic	FAP	NCT01960348 (Apollo)
	Revusiran	Sanofi/Alnylam	Transthyretin RNAi therapeutic	FAC	NCT02319005 (Endeavour)
	NEOD001	Prothena	Anti-beta-amyloid MAb	AL amyloidosis	NCT02312206 (Vital)
	Ninlaro	Takeda	Proteasome inhibitor	AL amyloidosis	NCT01659658 (Tourmaline-AL1)
Phase II	Zydelig	Gilead Sciences	PI3k-delta inhibitor	AL amyloidosis	NCT02590588
	Treanda	Teva/Astellas	Alkylating agent	AL amyloidosis	NCT01222260
	Revlimid	Celgene	Immunomodulator	AL amyloidosis	NCT00564889
	Pomalyst	Celgene	Immunomodulator	AL amyloidosis	NCT01570387
	SOM0226	SOM Biotech	Metabolic disease agent	FAP	NCT02191826
Phase I	MAb-11-1F4	NCI	Chimaeric amyloid-reactive MAb 111F4	AL amyloidosis	NCT02245867
	Kyprolis	Amgen/Ligand	Proteasome inhibitor	AL amyloidosis	NCT01789242
	GSK2315698	GlaxoSmithKline	Serum amyloid P component depleter	Systemic amyloidosis	NCT01777243
	GSK2398852	GlaxoSmithKline	Anti-serum amyloid P component MAb	Systemic amyloidosis	NCT01777243
	GSK3039294	GlaxoSmithKline	Serum amyloid P component depleter	Systemic amyloidosis	NCT02603172
	ALN-TTRsc02	Alnylam	Transthyretin RNAi therapeutic	Transthyretin amyloidosis	NCT02797847
FAP:Familial amyloid polyneuropathy, FAC: Familial amyloid cardiomyopathy					

Also in phase III is Prothena's NEOD001, a monoclonal antibody targeting misfolded proteins being tested in AL amyloidosis, which occurs when plasma cells produce antibodies with misfolded light chains, which are deposited as amyloid in organs.

Enrolment into Prothena's phase III Vital trial is expected to complete in the second quarter of next year, while topline results from its phase IIb Proto study are expected late in the year.

As of March the company had $474m in cash, including $129m net from an equity offering in January. Credit Suisse says peak sales could reach $1.85bn by 2030.

Takeda's Ninlaro is also being tested in AL amyloidosis, and received breakthrough therapy designation at the end of 2014. The phase III Tourmaline-AL1 study tests Ninlaro in combination with dexamethasone, and is estimated to complete in August 2018.

Ninlaro is marketed for multiple myeloma – a cancer of plasma cells; about 10-15% of patients with this disease also develop AL amyloidosis.

Even earlier

Celgene is also trying out the multiple myeloma treatment approach, testing Revlimid and Pomalyst in phase I/II trials. Meanwhile, Gilead is recruiting a small phase II trial testing Zydelig, its chronic lymphocytic leukaemia treatment. The primary completion date is October 2018. Teva's Treanda, also on the market for

CLL, is in a phase II amyloidosis trial that could read out by the year end.

Glaxo's assets are in phase I; two are serum amyloid P (SAP) component depleters and one is a monoclonal antibody. SAP binding stabilises amyloid fibrils, aiming to deplete circulating SAP, enabling injected anti-SAP antibodies to reach residual SAP in amyloid deposits. An open-label phase I trial in 15 patients triggered clearance of deposits from the liver.

The only marketed product, Pfizer's Vyndaqel, has been on sale in Europe for FAP since 2011. However, it received a US complete response letter back in 2012, with the FDA requesting a secondary efficacy study (*Alnylam pushes forward in amyloidosis after Pfizer set back, July 16, 2012)*. A phase III trial called ATTR-ACT completed its 400 patient enrolment last year while an open label extension study in 330 patients with transthyretin cardiomyopathy is to start recruiting this month.

Few analysts have forecasts for Vyndaqel, but those at Credit Suisse expect sales of $304m by 2022. With little news on its status in the US, and with Alnylam potentially gaining approval within two years, the race to market will be watched with interest.

Disease Condition	**Precursor Protein**	**Organs Affected**
ATTR amyloidosis (also called TTR amyloidosis) Includes FAP and FAC	Transthyretin (TTR) – genetic 'variant' type	Nerves Heart Carpal tunnel in the wrist Gastrointestinal tract Sometimes: Eye, Kidneys, Thyroid, Adrenals, Blood vessels
AL amyloidosis (the most common type of amyloidosis)	Monoclonal Immunoglobulin (antibody) Light chains	Kidney Heart Nerves Gastrointestinal tract Skin Tongue (macroglossia-enlarged tongue) Joints
AA amyloidosis	Serum amyloid A protein	Kidney Gastrointestinal tract Liver
Source:http://ttrstudy.com/attr-amyloidosis/		

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