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Therapy focus – Clinging to options in Friedreich’s ataxia

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Before the end of the year phase III results are expected from the most advanced pipeline project Actimmune, for the inherited neuromuscular disorder Friedreich’s ataxia. This interferon developed by Horizon Pharma has been on the market for two other genetic disorders for over a quarter-century.

As is often the case with rare diseases clinical setbacks in Friedreich's have been rife, but delving into the pipeline sees private and larger companies such as Shire and Abbvie hoping to make headway (see table). Targets include decreasing oxidative stress or increasing levels of the missing protein, while gene therapy is at its very early stages.

Mutated gene

Friedreich’s ataxia (FA) is an inherited neurodegenerative disease that causes progressive damage to the nervous system, caused by a mutation in the gene encoding the frataxin protein necessary for proper mitochondrial function.

It leads to degeneration of the peripheral nerves and spinal cord, resulting in difficulties walking and impaired sensory functions. Heart disorders such as atrial fibrillation, along with type 1 diabetes, can affect patients, but the disease does not affect cognitive function.

Symptoms typically appear between the ages of 5 and 15 years, and the average life expectancy is 37. With a lack of medical treatments patients are monitored for symptom management and offered occupational therapy.

Santhera’s idebenone received conditional market approval as Catena for FA in Canada back in 2008, but was removed from the market five years later because of a subsequent clinical trial failure *(Catena once again Santhera's downfall, May 20, 2010).*

Actimmune is the most advanced candidate in the pipeline, and is marketed for the chronic granulomatous disease and severe malignant osteopetrosis. In animal models of FA it has increased frataxin levels.

A phase III trial, Steadfast, completed enrolment in May having recruited 90 patients aged 10-25 who will receive Actimmune or placebo three times a week for 26 weeks. The primary endpoint is the change from baseline in neurological outcome as measured by a modified version of the FA rating scale (FARS).

A phase II trial in 12 patients showed improvements in FARS scores but could not demonstrate a clear relationship to changes in frataxin levels. Actimmune was well tolerated with no serious adverse events. It has orphan drug designation for FA and fast-track status.

Despite being such an elderly drug it has forecast sales of $745m in 2022, according to consensus from *EvaluatePharma*, with $249m expected in FA. Last year sales were $107m. It is holding off biosimilar competition for now, thanks to its composition of matter patent, though this expires in 2022.

Protein target

Also trying to increase frataxin levels are projects from Jupiter Orphan Therapeutics and Biomarin. Jupiter’s JOT101 is a proprietary formulation of resveratrol, a natural compound present in grapes and red wine, and in January the company signed a licensing agreement with the Murdoch Children’s Research Institute in Australia.

An open label phase I/II trial in 24 patients was carried out by Murdoch. This found no effect on frataxin levels, but improvements were observed in neurological function in the high-dose group. Gastrointestinal side effects were common.

Biomarin is further behind, having acquired Repligen’s HDAC inhibitor programme in 2014. Repligen completed a phase I Italian trial with oral RG2833, which at high doses caused an increase in frataxin mRNA, a measure of

gene expression. Little news has emerged since then, but the Freidreich's Ataxia Research Alliance website notes that Biomarin is identifying follow-on versions.

Selected Friedreich's ataxia pipeline				
Status	**Project**	**Company**	**Pharma class**	**Trial ID**
Phase III	Actimmune	Horizon Pharma	Interferon gamma	NCT02415127 OLE NCT02593773 Safety extension NCT02797080 Phase II NCT01965327
Phase II	EPI-743	Edison Pharmaceuticals	NADPH quinone oxidoreductase 1 modulator	NCT01962363 NCT01728064
	Epicatechin	Cardero Therapeutics	Mitochondria targeted therapy	NCT02660112
	Omaveloxolone	AbbVie/Reata Pharmaceuticals	Nuclear factor erythroid derived 2 activator	MOXIe study NCT02255435
	JOT101	Jupiter Orphan Therapeutics	Sirtuin activator	Murdoch Children's Research Institutie trial NCT01339884
	Nicotinamide	Imperial College London	Vitamin B3	NCT01589809
	RT001	Retrotope	Free radical scavenger	NCT02445794
Phase I	Oxigon/SHP622	Shire	Beta-amyloid aggregation inhibitor	NCT01898884
	RG2833	BioMarin Pharmaceutical/Repligen	Histone deacetylase inhibitor	-

Another popular area of development in FA is looking at decreasing oxidative stress or increasing mitochondrial function. Bigger pharma companies, including Abbvie and Shire, are active here.

Reata's omaveloxolone is an activator of Nrf2, a protein whose signalling is impaired in FA, resulting in an impairment of antioxidant defence mechanisms. The MOXIe phase II/III study started enrolling last year and aims to recruit 56 patients aged 16-40. Oral omaveloxolone, also known as RTA 408, is pitted against placebo in the dose-escalation study.

Reata completed its $61m IPO in May, and while shares have since risen 35% the company had to float at a 27% discount to its announced price. Abbvie's involvement stems from historic Abbott licensing agreements, and Abbvie now shares omaveloxolone development costs with Reata.

Meanwhile, Shire gained SHP622, also known as Oxigon, through its acquisition of Viropharma, which licensed rights from Intellect Neurosciences. In a phase Ib trial completed in July last year in 55 adults with FA SHP622 was well tolerated, but there were no clinically meaningful differences between treatment and placebo. According to Shire's half-year report the group is determining a path forward for the programme.

Small private companies including Edison Pharmaceuticals and Retrotope are also investigating oxidative damage as a target in FA.

Root cause

Gene therapies feature in preclinical trials, but this area has struggled to make headway in many disorders.

Voyager Therapeutics signed a $100m deal with Sanofi last year over four early-stage gene therapy assets, including one in FA. The company completed its $70m IPO towards the end of the year. Agilis Biotherapeutics and Adverum Biotechnologies are also in the space. The latter, once known as Avalanche Biotechnologies, suffered a huge setback when its wet AMD gene therapy failed.

While gene therapy remains a long way off perhaps Horizon's candidate can be the success the space so desperately needs.

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