Evaluate Vantage

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Therapy focus – No safe haven for bio in spinocerebellar ataxia

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This week brought fresh evidence of the perils of pinning hopes on a late-stage study readout, as investors in Biohaven – a biotech that completed one of 2017's biggest floats just five months ago – found out to their cost.

Still, the group's rare disease focus clearly struck a chord, as shown by its market cap breaching $1bn in the run-up to Monday's phase II/III failure of trigriluzole. The extent to which this reflects the value of spinocerebellar ataxia, the rare disease in question, is not clear, but the lack of treatments for it in the west is still spurring a handful of companies (see table below).

One of the problems is that spinocerebellar ataxia is actually a group of conditions, each of which could arguably be called a disease in its own right. Biohaven's trial, in 141 adults, allowed enrolment as long as a patient had, or was suspected to have, one of seven of the 29 or so genetic variants.

The diseases manifest themselves similarly, in that subjects slowly lose co-ordination in gait, speech, and hand and eye movement. As Biohaven found, proving efficacy is tricky: versus placebo trigriluzole failed to improve either the Scale for the Assessment and Rating of Ataxia or Patient's Global Impression of Change.

Placebo response?

Biohaven blamed an unusually high placebo response, but admitted that the negative data did not support trigriluzole's continued development as a symptomatic treatment. However, it is clear that treatments are needed – the only approved drug, Mitsubishi Tanabe's Ceredist, is only available in Japan.

It might be that an early government effort there spurred development – Japan's ministry of health and welfare had designated Ceredist an orphan drug as long ago as 1993. Indeed, one of the most advanced current industry projects, Shionogi/Kissei's rovatirelin, is in phase III development only in Japan.

Like Ceredist, rovatirelin is an analogue of thyrotropin-releasing hormone, which has been found to benefit patients with spinocerebellar ataxia. Several mechanistic approaches are being used against the condition, perhaps betraying a fundamental lack of understanding of its basis.

Biohaven's trigriluzole is a glutamate release modulator, like Riluzole, a drug marketed for amyotrophic lateral sclerosis. However, Riluzole is not being studied for spinocerebellar ataxia, and Biohaven says trigriluzole has better oral bioavailability and lacks effects on liver function.

Some hope in treating spinocerebellar ataxia?					
Project	**Company**	**Pharmacology class**	**Trial ID**	**Data due**	**Note**
Phase III					
Rovatirelin	Shionogi/Kissei	Thyrotrophin-releasing hormone analogue	NCT02889302	Nov 2018	Japan only; same mechanism as Ceredist
EryDex	Erydel	Corticosteroid	NCT02770807	Aug 2018	Focus is ataxia telangiectasia
Trigriluzole	Biohaven Pharmaceutical	Glutamate modulator	NCT02960893	Failed	Remains in open-label extension until Q4 2018
Phase II					
Ampyra	Acorda Therapeutics	Potassium channel blocker	NCT01811706	Completed	Marketed for multiple sclerosis; investigator-sponsored trial
Gammagard Liquid	Shire	Immunoglobulin	NCT02287064	Dec 2016	Marketed IVIG; investigator-sponsored trial
Cabaletta (trehalose)	Bioblast Pharma	Transcription Factor EB activator	NCT02147886	Completed	Also in more advanced trials in muscular dystrophy
Stemchymal	Steminent Biotherapeutics	Stem cell therapy	NCT02540655	Nov 2017	Also in less advanced trials in Alzheimer's, Parkinson's & OA of the knee
Source: EvaluatePharma.					

Two other marketed drugs that are in mid-stage trials for spinocerebellar ataxia are Acorda's Ampyra and Shire's Gammagard Liquid. The former has been shown in multiple sclerosis – its approved indication – to improve standing balance, while the latter, an IVIG, plays into the theory that inflammation might play a role in severe ataxias.

Even stranger is the use of trehalose, a sugar more commonly used as a protein stabiliser, in spinocerebellar ataxia; this is the focus of Bioblast Pharma, specifically in the disease's type 3 variant, where an open-label phase II study recently showed stabilisation of disease scores.

Perhaps the most advanced concept scientifically is an allogeneic stem cell product called Stemchymal, in development by Steminent Biotherapeutics. This showed a promising effect on the Scale for the Assessment and Rating of Ataxia in an early trial, and a phase II study is enrolling.

And Erydel is looking at a corticosteroid, though its focus is now on ataxia telangiectasia, which like Friedreich's ataxia is a distinct autosomal recessive disorder in which ataxia plays a prominent part. As Friedreich's has shown, this is a tough area for developers (*Friedreich's failure highlights thinning pipeline, June 2, 2017*).

At least Biohaven investors can take comfort in the fact that their company has not pinned its hopes entirely on spinocerebellar ataxia; trigriluzole is also being studied in obsessive-compulsive disorder and ALS, and the group has a range of CGRP-targeting projects for migraine.

While on Monday its stock initially lost 26% it recovered later, but was off another 7% yesterday. An open-label extension might allow for a signal to be detected when it reads out in a year's time.

Still, it might be the case that progress here will not be made until the disease is more accurately defined, and specific patients can be recruited into studies with harder endpoints.

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