Evaluate Vantage

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Biogen leads the way in renewed amyotrophic lateral sclerosis push

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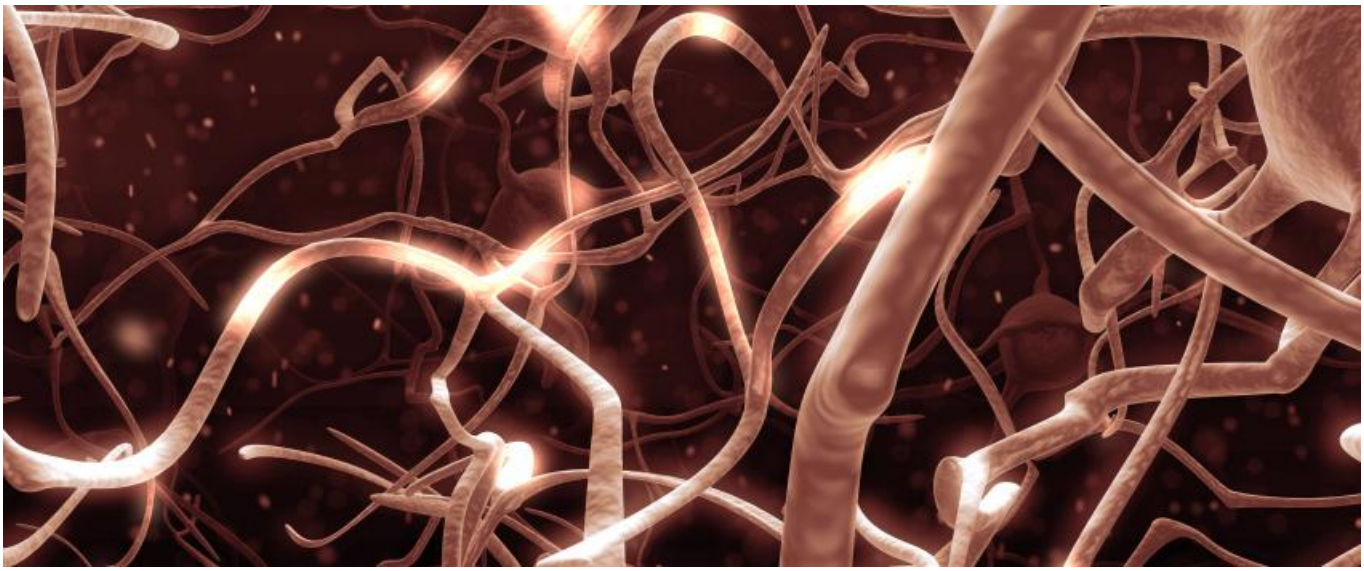

The company has quietly emerged as the key player to watch in an area that has seen several setbacks of late.

One of the highlights of Biogen's second-quarter results call yesterday concerned the group's commitment to amyotrophic lateral sclerosis: with one pivotal trial and two projects in early development Biogen has quietly become one of the leaders in the search for a treatment.

It is, of course, not alone, and the industry pipeline reveals near-term study readouts from Brainstorm Cell Therapeutics, Gilead and Revalesio. New trials are getting under way, too, showing that companies are not allowing recent setbacks to distract them from working on this intractable motor neurone disease.

Among the setbacks, Mallinckrodt this month halted the phase II Pennant study of H.P. Acthar Gel on the advice of a data-monitoring board, and Biohaven received a US complete response letter for Nurtec over manufacturing issues. Nurtec is a formulation of riluzole, one of two drugs approved for treating ALS.

Three assets

This has not deterred Biogen, which yesterday highlighted two assets targeting genetic forms of ALS: tofersen, an anti-SOD1 mRNA, should yield results from the potentially pivotal Valor trial in 2021, at the same time as the anti-C9orf72 oligo BIIB078 generates phase I data. Both are partnered with Ionis.

A separate phase I project, BIIB100/KPT-350, was licensed from Karyopharm last year. This is a small-molecule inhibitor of XPO1, a mechanism that Biogen hopes can slow the progression of sporadic ALS.

While the pivotal tofersen readout might now be the most keenly awaited ALS catalyst, it will be preceded by results of a phase III study of Brainstorm's cell therapy NurOwn Program One. The micro-cap company is perhaps most famous for mooting the idea of turning a profit from the controversial US Right to Try scheme.

Another controversial late-stage project is AB Science's masitinib, which as Masican has been in development for cancer. The EU has rejected mastinib for ALS, but trumpeting positive phase II/III data AB intends to start another pivotal study, in 495 subjects, in the second half of this year.

Mid-stage ALS pipeline (selected projects, excluding riluzole formulations)				
Project	**Mechanism**	**Company**	**Trial ID**	**Note**
Phase III				
NurOwn Program One	Cell therapy	Brainstorm Cell Therapeutics	NCT03280056	200 subjects, ends Jul 2019
Tofersen	SOD1 inhibitor mRNA	Biogen/Ionis	NCT02623699 (Valor)	144 subjects; ends May 2020, data 2021
Simdax po (levosimendan)	PDE3 inhibitor	Orion	NCT03505021	450 subjects, ends Aug 2020
Arimoclomol citrate	SOD1 chaperone	Orphazyme (ex Cytrx)	NCT03491462	213 subjects, ends Dec 2020
Alsitek (masitinib)	CD117, FGFR3 & PDGFR antagonist	AB Science	NCT03127267	495 subjects, starts H2 2019
Phase II				
Ketas (ibudilast/MN-166)	LTD4 receptor antagonist	Medicinova	NCT02238626 (IBU-ALS-1201)	71 subjects, completed; pivotal trial planned
RNS60	GPCR antagonist	Revalesio	NCT03456882	142 subjects, completed Apr 2019
EPI-589	Unknown	Bioelectron Technology/Sumitomo Dainippon	NCT02460679	20 subjects, completed 2018
Ranexa (ranolazine)	FFA antagonist	Gilead	NCT03472950	20 subjects, ends Oct 2019; drug available for angina
ILB	Aryl hydrocarbon receptor, CPT & COX inhibitor	Tikomed	NCT03705390	15 subjects, ends Mar 2020
IPL344	AKT stimulant	Immunity Pharma	NCT03755167	15 subjects, starts this year after evidence in compassionate use
AMX0035 (TUDCA + PB combo)	Unknown	Amylyx Pharmaceuticals	NCT03488524 (Centaur-Ole)	132 subjects, ends Jan 2020
CNM-Au8	Elemental gold nanocrystals	Clene Nanomedicine	NCT03843710 (Repair-ALS)	24 subjects, starts this year
Source: EvaluatePharma.				

Of course, investors will bear in mind that ALS remains an intractable disease, as evidenced by several mid-stage studies falling by the wayside.

Examples include phase II trials of Neuralstem's NSI-566, Genervon's GM604 and Medday's Qizenday. All of these ended in the past four years with no news about data or further plans, suggesting that these projects have at best been deprioritised in ALS.

Among other blows to this sector, Cytokinetics' Fortitude-ALS study of reldesemtiv failed two months ago; the asset had been selected as a follow-on to the company's tirasemtiv, which flunked a pivotal ALS trial two years ago (*Therapy focus – Cytokinetics crash puts spotlight on new ALS approaches, November 22, 2017*).

On the other hand, Bioelectron Technology last year claimed a mid-stage win with EPI-589, a project with an unknown pharmacology that the company says targets "oxidoreductase enzymes known to be critical to the regulation of inflammation".

Revalesio recently completed a study of the GPCR antagonist RNS60, so investors should look out for these data, while a trial of Gilead’s free fatty acid receptor antagonist Ranexa ends in October; the latter is an investigator-sponsored test of a drug available for chronic angina.

It seems apparent that work continues into an astonishing array of possible mechanisms of action. The enthusiasm should be welcomed, though it perhaps betrays a fundamental lack of understanding of the underlying causes of ALS.