

Therapy focus - Cytokinetics crash puts spotlight on new ALS approaches



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The phase III failure of Cytokinetics' amyotrophic lateral sclerosis candidate tirasemtiv – despite endpoint tinkering – highlights once again how few options there are for patients with this intractable disease.

But a look at the mid-stage pipeline shows that companies are still willing to take a chance in this high-risk/high-reward field. A slew of different approaches are being tried, with readouts on the horizon for Neuraltus's macrophage regulator NP001 and Medicinova's MN-166, which the company describes as a glial attenuator (see table below).

Still, the next most-advanced project in the pipeline is more familiar, not least because it has been tested in at least 10 separate indications by its developer, AB Science. Masican is already filed for amyotrophic lateral sclerosis (ALS) in Europe on the back of a [phase II/III study](#) – which was positive at the higher dosed used – and another phase III trial could yield data next year. It is unclear if the company will need to wait for these before filing Masican for ALS in the US.

ALS projects in active phase II and III trials

Project	Company	Pharma class	Trial(s)	Primary completion
Phase III				
Tirasemtiv	Cytokinetics/Astellas	Troponin activator	Vitality-ALS, NCT02496767	Failed, discontinued
Masican	AB Science	c-kit tyrosine kinase, PDGFr & FGFR 3 inhibitor	NCT03127267	Sep 2018
Nurown Program One	Brainstorm Cell Therapeutics	Mesenchymal bone marrow stromal cell therapy	NCT03280056	Apr 2019
Phase II				
GM604	Genervon Biopharmaceuticals	GM6 analogue	NCT01854294	Reported, phase III to start in 2017
Arimoclomol citrate	Orphazyme	SOD 1 chaperone	NCT00706147	Reported, phase II/III to start H2 2018
MD1003	Medday Pharmaceuticals	Vitamin B	NCT03114215	Jun 2017
NP001	Neuraltus Pharmaceuticals	Macrophage regulator	NCT02794857	Sep 2017
MN-166	Medicinova	LTD4 antagonist	NCT02238626	Dec 2017
EPI-589	Sumitomo Dainippon Pharma	CNS agent	NCT02460679	Feb 2018
FLX-787	Flex Pharma	TRPA 1 antagonist & TRPV 1 agonist	Commend, NCT03196375	Jun 2018
CK-2127107	Cytokinetics/Astellas	Troponin activator	NCT03160898	Jul 2018
AMX0035	Amylyx Pharmaceuticals	CNS agent	NCT03127514	Dec 2018
Albutein	Grifols	Human albumin	NCT02872142	Jan 2019
H.P. Acthar Gel	Mallinckrodt	Adrenal corticotropin hormone	NCT03068754	Mar 2020

Source: EvaluatePharma, clinicaltrials.gov.

Stem cell-based approaches were once touted as a potential way forward in ALS, but the only such project that appears to be in active trials is Brainstorm Cell Therapeutics' Nurown Program One ([Therapeutic focus - Cell therapies await real answers in ALS, March 25, 2015](#)).

Neuralstem is still developing its stem cell candidate, NSI-566, according to a [November update](#), but its most recent ALS trial passed its completion date in 2015 and its status is unknown.

Meanwhile, another cell therapy project, Q Therapeutics' Q-Cells, is has yet to begin its planned phase I/II trial, [according to Clinicaltrials.gov](#).

Progressing

While this area of research seems to have stalled, there are plenty of other approaches in play, and the phase III pipeline could soon be bolstered by two more projects in the shape of Orphazyme's arimoclomol citrate and Genervon's GM604.

The former had phase II data in patients with SOD1 mutations back in December 2016 but, according to the company's website, is not due to start phase III development until the second half of 2018. This 200 to 300-

patient study will up the dose of arimoclomol to 400mg three times daily, from 200mg three times per day in phase II.

Meanwhile, Genervon's phase IIa study of GM604 read out in March, and the group said it hoped to begin phase III this year. This has yet to happen, but with GM604 also being developed for multiple sclerosis perhaps the company's attention has been diverted elsewhere.

MS is also the main focus for Medday Pharmaceuticals' MD1003; a phase II trial of the project in ALS was due to complete in June, according to [Clinicaltrials.gov](https://clinicaltrials.gov), but the company does not appear to have reported results.

It could be beaten to the punch by Neuraltus Pharmaceuticals, which finished enrolment into its phase II trial of NP001 in July and said it hoped to report topline data in the first quarter of 2018.

Next up

As for Cytokinetics, it has quickly pivoted to its next-generation troponin activator, CK-2127107, which is in phase II.

This is some consolation after the company's stock crashed 26% yesterday on news that the Vitality-ALS trial of tirasemtiv, its lead project, had failed.

The miss came despite a change in the study's primary outcome to slow vital capacity - a measure that showed improvement in a phase II trial that also failed to meet its primary endpoint ([Upcoming events - Arctic readout for Imfinzi while Cytokinetics tries again in ALS, October 13, 2017](#)).

Cytokinetics believes that CK-2127107 will be better tolerated and potentially more effective than tirasemtiv. This will be put to the test when phase II data report next year, and the company will no doubt be wary of making the same mistake again and moving the project forward without a strong efficacy signal.

Orion should also take note: this company's oral levosimendan, known as ODM-109, failed in phase II, but the group said the data were nevertheless promising and that it would continue development.

The US FDA has shown itself to be relatively lenient in ALS, with the approval of Mitsubishi Tanabe Pharma's Radicava earlier this year on limited data providing a case in point. But drug development in central nervous system disorders is often tricky, and Cytokinetics might have taught its ALS rivals a lesson about when to press on - and when not to.

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