Evaluate Vantage

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Radicava bags approval without a radical benefit

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Amyotrophic lateral sclerosis (ALS) patients will no doubt be relieved to have a new option after the FDA approved Mitsubishi Tanabe Pharma's edaravone, known in the US as Radicava. But with a $145,000-per-year price tag, and no proof yet that it improves survival, getting it paid for might be a different matter.

The FDA was obviously keen to get Radicava, a free-radical scavenger, on the market – it took the unusual step of asking Mitsubishi to file it on the back of a six-month Japanese trial, and one that could only show a slower progression of disability with Radicava versus placebo. The hunt is still on for something better, and there are several ALS candidates in the late-stage pipeline that could offer hope (see table below).

Radicava's uptake could also be hindered by the availability of generic riluzole – the active ingredient of Sanofi's Rilutek, the last ALS agent to get FDA approval in 1995.

Survival

In fairness, proving a survival benefit in ALS is tough: the most advanced project after Radicava, AB Science's Masican, could not do so in its pivotal study. AB blamed the fact that ALS trials are not long enough for many patients to reach this endpoint, reducing the statistical power.

Masican has succeeded on the same primary endpoint as Radicava, showing improvement on the ALS functional rating scale-revised (ALSFRS-R), but AB has not yet reported detailed data (*AB Science claims a positive result in masitinib ALS study, April 19, 2016*). Full results will be presented at the European Network for the Cure of ALS (ENCALS) meeting, being held on May 18-20.

Masican is thought to work by inhibiting the proliferation of glial cells, the support cells in the brain, including the neurotoxic aberrant microglial cells that have been linked with disease development. The diverse range of mechanisms being tried in ALS reflects the difficulty of treating the disorder, as well as a lack of understanding of its causes.

Late-stage ALS pipeline

Status	Project	Company	Mechanism
Filed	Masican	AB Science	C-kit tyrosine kinase, PDGFr & FGFR 3 inhibitor
Filed (South Korea)	YYB-103	YooYoung Pharmaceutical	Undisclosed
Phase III	Tirasemtiv	Astellas Pharma/Cytokinetics	Troponin activator
Phase III	Arimoclomol citrate	Orphazyme	SOD 1 chaperone
Phase III	HYNR-CS	Corestem	Stem cell therapy

Source: EvaluatePharma

AB has filed Masican for ALS in the EU, where a decision is expected by the end of this year; as for the US, the company has said it will discuss its next steps with the FDA.

Radicava's approval suggests that the agency is inclined to be lenient, likely because of a paucity of other therapies. Although Mitsubishi's product has not demonstrated a survival benefit, it has shown a significant improvement over placebo on both the ALSFRS-R and a quality of life questionnaire known as ALSAQ40 at 24 weeks, and this effect was sustained over 12 months in an extension study.

24-week results of MCI-186-J19 trial of Radicava		
Endpoint	**Difference vs placebo**	**p value**
ALSFRS-R	2.49 ± 0.76	0.001
ALSAQ40	-8.79 ± 4.03	0.031

That this was enough for the FDA could spell good news for AB Science's project. But, on the evidence available, neither appears to be a disease-modifying therapy. Any product that can be proven to prolong survival would dramatically change the ALS landscape.

Project	**Study**	**Trial ID**
Radicava	MCI-186-J19	NCT01492686
Masican	AB10015	NCT02588677

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