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Amylyx changes its mind about an early filing

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The group hopes phase 2 data will back approval for its amyotrophic lateral sclerosis project AMX0035 after all.

Five months ago Amylyx Pharmaceuticals said it would have to wait for results from an upcoming phase 3 trial before filing its amyotrophic lateral sclerosis project AMX0035 with the FDA. Now it has said a submission is due "in the coming months" based on data from the phase 2 Centaur trial.

What changed? The data package is essentially the same, but Amylyx execs cited "recent discussions" with the FDA including a pre-NDA meeting in July. "The FDA will never explicitly say much about whether something's approvable or not, because that's the whole point of the review process," the group's co-chief executive officer, Justin Klee, tells *Evaluate Vantage*. "But they made it clear that they thought we should submit an NDA and that it would merit a review."

As ever the regulator has made no puiblic statement on the matter, so there is only the company's word to go on for now. Mr Klee adds that the agency stressed the importance of data from the phase 3 study, Phoenix, which is set to start to start treating patients in the next couple of months. Amylyx also hopes to run a US expanded-access programme in parallel with the pivotal study.

But it will be a while before Phoenix reads out: its primary endpoint, the amyotrophic lateral sclerosis functional rating scale-revised (ALSFRS-R), is being measured over 48 weeks. Furthermore, Phoenix seeks to enrol 600 patients, and recruitment into ALS trials has typically been "fairly slow", admits Josh Cohen, Amylyx's other co-chief exec. "We don't know if recruitment will take a year or two years. I guess we'll find out as we start recruiting."

Full, not accelerated?

Still, Phoenix might not be vital for AMX0035's US green light, if all goes to plan. Mr Cohen believes that if the project does get the nod this will likely be a full approval, rather than the accelerated type that recently saw Biogen's Alzheimer's drug Aduhelm reach the market.

"The accelerated pathway is supposed to be for when you hit a surrogate rather than an actual clinical endpoint," says Mr Cohen. "We've shown effects on function and survival. We don't really have a surrogate."

The obvious conclusion to draw from the privately held Amylyx's U-turn is that the company hopes to benefit from a lenient-looking FDA, at least when it comes to neurology projects. But the co-chiefs refuse to weigh in on whether the agency has indeed lowered the bar. "It's hard for us to speculate, especially given that we have just the one programme in front of them," says Mr Klee.

Instead, he points to an understanding of the unmet need in ALS, saying the FDA had always been up for a discussion about how to accelerate AMX0035's filing.

Perhaps Amylyx's case here has been strengthened by several recent late-stage failures in ALS, for which no disease-modifying therapies are available. Brainstorm's NurOwn, Orphazyme's arimoclomol and, most recently, Astrazeneca's Ultomiris have all flunked pivotal studies in the past year.

Brainstorm said it would push ahead with a filing, but the FDA took the unusual step of putting out a statement saying the NurOwn data were insufficient for approval.

The next big hope is Biogen and Ionis's tofersen, which is set to yield data from the phase 3 Valor study this half.

Centaur success

Still, tofersen only takes aim at ALS patients with Sod1 mutations, who account for around 2% of those with the disease.

AMX0035, meanwhile, has the potential to help all patients. The project, a combination of sodium phenylbutyrate and taurursodiol, is thought to reduce endoplasmic reticulum stress and mitochondrial dysfunction, preventing the death of neurons.

The phase 2 Centaur study found a statistically significant improvement with AMX0035 versus placebo on the ALSFRS-R over 24 weeks and in overall survival (*Amylyx provides hope in amyotrophic lateral sclerosis, October 21, 2020*).

But there are reasons for caution: the therapeutic effect has been termed modest, the trial was small, in just 137 patients, and there was a higher dropout rate with AMX0035 than placebo due to adverse events, most commonly diarrhoea.

Ideally, a larger trial should be required to support approval, but maybe the FDA is of the opinion that, with few options available for ALS patients, time is of the essence.

Of course, it is possible that the agency, which does not disclose details of its meetings with companies, is not as positive about AMX0035 as Amylyx has implied. The ALS community, which has had its hopes dashed many times, will find out when the FDA comes to a decision on the project's approvability.