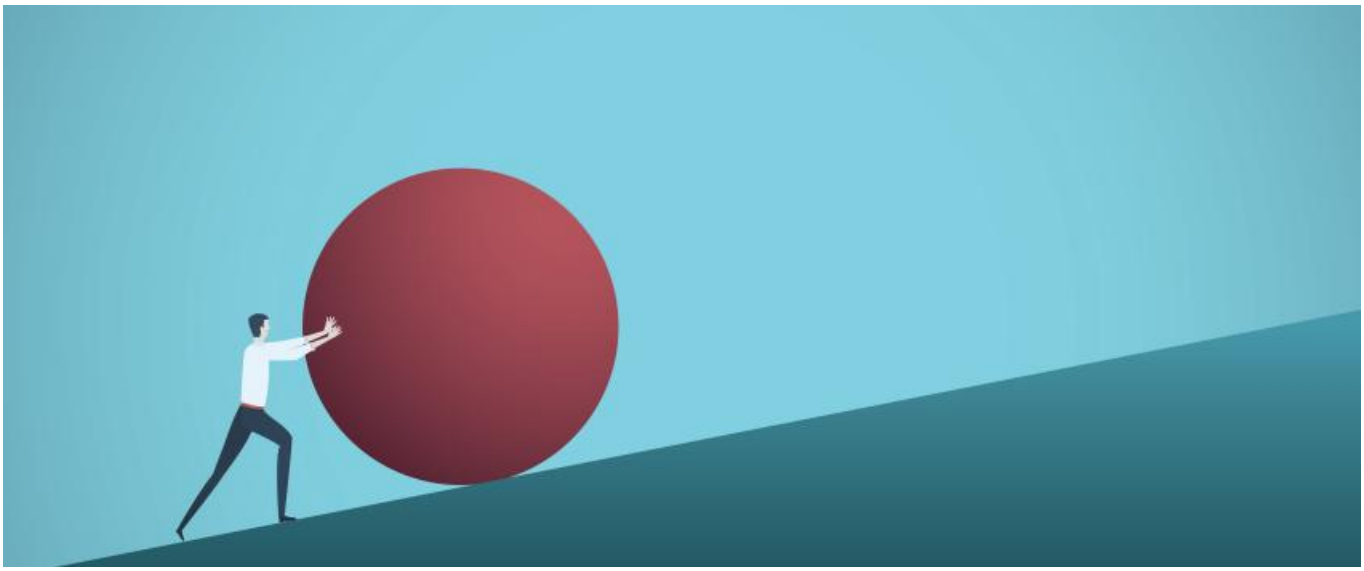
Evaluate Vantage

March 29, 2022

Amylyx faces an uphill battle

Madeleine Armstrong



Briefing documents show why the FDA should await more data on the ALS project, but will it bow to patient pressure?

FDA approval decisions on neurology projects are rarely without controversy these days, and the case of Amylyx's AMX0035 looks like being no exception. Briefing documents released by the FDA yesterday painted a damning picture, throwing into doubt the company's claims of functional and survival benefits with the amyotrophic lateral sclerosis project in phase 2.

The prudent thing would be to wait for data from a pivotal trial that Amylyx has already started. However, the FDA is facing pressure from ALS patient advocates to approve AMX0035 given the lack of other options in the disease. The final decision will be made in the shadow of the Aduhelm controversy, of course, and provide another test of the agency's willingness to grant approval on the back of questionable data.

Still, the cases of AMX0035 and Aduhelm are not completely analogous – the former, at least, is relatively safe, the briefing documents concluded.

But that was where the good news ended for Amylyx, whose stock fell 36% yesterday. In fact, the documents were so negative that it is unclear why the FDA had asked the company to file for approval based on the phase 2 data – a position that was confirmed yesterday (*Amylyx changes its mind about an early filing, September 15, 2021*).

The FDA had originally said Amylyx would have to wait for results from the phase 3 Phoenix trial before submitting AMX0035. What was behind the agency's change of heart, if it was unconvinced by the existing data?

It has recently emerged that lobbying from the ALS Foundation played a big part in the U-turn, which begs the question, as posed by Leerink analysts: "Is the adcom scheduled just to make it easier to reject a drug that [the FDA is] receiving so much political pressure to approve?"

The understandable argument from ALS patients is that they do not have the luxury of time – Phoenix is not set to complete until late 2023. And these patients have had several disappointments lately, including yesterday's discontinuation of Ionis and Biogen's BIIB078.

Data doubts

However, with the question marks hanging over AMX0035, it is hard to justify its approval at present. The data package is based on the phase 2, placebo-controlled Centaur study and its open-label extension trial.

As previously reported, Centaur met its primary endpoint, showing a 2.32-point difference between AMX0035 and placebo on the ALS functional rating scale-revised (ALSFRS-R) rate of decline – hitting statistical significance with a p value of 0.034. This benefit was previously described as modest, spurring investor jitters ahead of the adcom.

However, the FDA has more fundamental issues, with various questions about Amylyx's statistical analyses and the rigour of this result. Perhaps most damning was the fact that the company used a modified intent-to-treat population that excluded two AMX0035-treated patients who died before post-baseline ALSFRS-R could be measured.

Including these patients, as well as using the joint rank analysis of ALSFRS-R and death that the FDA had recommended, pushed the p value to 0.079; in other words, not statistically significant.

There are those who believe that a fairly narrow miss might still be enough, including Evercore ISI's Umer Raffat and Mike DiFiore.

But Amylyx's claim of a survival benefit with AMX0035, which came from the open-label study, is also looking shaky. The reviewers descried this result as "not persuasive", and concluded: "The modest survival benefit seen may potentially be due to underlying disease heterogeneity rather than an effect of the drug."

Panellists at the adcom, taking place tomorrow, will vote on just one question: whether the current data support a conclusion that AMX0035, a combination of sodium phenylbutyrate and taurursodiol, is effective in ALS. The answer seems obvious.

Ultimately, the FDA is facing a decision that will either further antagonise its critics or upset ALS patients. But if the agency wants to regain some credibility after the Aduhelm debacle it seems clear what it must do.