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AMX0035 Further Demonstrates Safety Profile in ALS, Alzheimer Disease

The findings in Alzheimer disease further elucidated the safety profile of AMX0035, as treatment emergent adverse events in the PEGASUS trial appeared to be largely disease driven.

New data from the phase 2/3 CENTAUR (NCT03127514) and phase 2 PEGASUS trials (NCT03533257) of AMX0035 (Amylyx Pharmaceuticals) support the investigational agent's overall safety and tolerability profile among patients with amyotrophic lateral sclerosis (ALS) and Alzheimer disease (AD), respectively.[1]

The findings, presented at the 2022 American Academy of Neurology (AAN) Annual Meeting, April 2-7, in Seattle, Washington, showed an adverse event (AE) rate that was similar between study drug and those on placebo. AMX0035, an orally administered, fixed-dose coformulation of sodium phenylbutyrate and taurursodiol, is currently under FDA review, with a PDUFA date set for June 30, 2022.

"In fatal diseases like ALS and AD, it is often difficult to distinguish between treatment-emergent adverse events (TEAEs) versus adverse events (AEs) that could either be attributed to the natural progression of the disease or the study medication," Machelle Manuel, PhD, head of Global Medical Affairs, Amylyx, told *NeurologyLive*®. "Our analyses of participants in both the CENTAUR and PEGASUS trials allowed us to draw comparisons to consider this differentiation."

CENTAUR was a phase 2/3 trial that comprised of 137 individuals with ALS who completed a 6-month randomized placebo-controlled period and were thus eligible to enroll in an open-label extension. In PEGASUS, 95 adults with dementia or late mild cognitive impairment due to AD were randomized to 24 weeks of treatment with either AMX0035 or placebo.

Across both studies, AMX0035 continued to show a safety profile similar to what was previously observed, with the majority of treatment-emergent AEs (TEAEs) gastrointestinal and no new safety signals. Diarrhea, and to a lesser extent, abdominal discomfort/pain, abdominal distension, and dyspepsia were more frequent in those on AMX0035 vs placebo. Despite the high rate of TEAEs, most of them were nonserious, mild or moderate in intensity, and assessed as unrelated to treatment with study medication.[1]

When comparing both trials, muscular weakness and falls were the most common in CENTAUR, which may suggest that that increased number of TEAEs in patients with ALS may be due to their natural disease progression. Manuel added that they were “encouraged” by these findings, and that "overall, these are important insights that further clarify the safety and tolerability profile of AMX0035 and help us continue to support those living with neurodegenerative diseases, including our clinical trial participants."

With only 2 FDA-approved therapeutics, the FDA’s impending decision on AMX0035 could have seismic effects on the ALS patient community. Amylyx’s new drug application, submitted in November 2021, was backed by data from CENTAUR that showed that the drug met its primary end point, demonstrating a 2.32 difference relative to placebo on ALS Functional Rating Scale-Revised (ALSFRS-R) over 24 weeks of treatment.[2]

In March 2022, a public hearing by the FDA’s Peripheral and Central Nervous System Drugs Advisory Committee added to the speculation of AMX0035’s future, voting that the current data is not sufficient in demonstrating efficacy. The committee voted 6-4 (6 no; 4 yes; 0 abstain) that the data from the trial and its open-label extension did not adequately establish the agent as an effective medication for the treatment of ALS.[3]

At AAN 2022, Justin Klee and Josh Cohen, the co-CEOs and co-founders of Amylyx, sat down to discuss the new data down to discuss the new data, along with their reactions to the Advisory Committee meeting. When asked how the findings further boost the drug’s profile, Klee said, "what we confirmed was that there appears to be a good safety profile, and the adverse events were seeing are consistent. These were generally things like diarrhea, which seems to resolve relatively quickly after initiation of therapy. In terms of increasing the profile of the therapy, I’d say we’re lucky that data for this therapy has already been published in the *New England Journal of Medicine.* We definitely plan to continue to analyze and publish, but I think it’s already quite a robust and rigorous study result."

The company also has an ongoing phase 3 study in ALS, PHOENIX (NCT05021536), which it hopes will continue to add to the drug’s efficacy and safety profile. This 48-week, randomized, placebo-controlled study will use ALSFRS-R as the primary end point, along with change in slow vital capacity as a secondary efficacy outcome. It plans to enroll 600 participants with definite or clinically probable ALS within 24 months of symptoms onset, an expansion from CENTAUR inclusion criteria.[4]

"We’re thrilled about the PHEONIX study,” Cohen added. “Ultimately, the prospect for a person with ALS is rapid disease progression and mortality. It’s likely that by the time PHOENIX reads out, much of a generation of ALS will have passed away. We feel that there’s a path to balance urgency and data."

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