



Amylyx – AMX0035 September 2020

Background

Amylyx Pharmaceuticals Inc. is a company that started in 2013 with the aim of testing a combination product called AMX0035 as a potential treatment for ALS and other neurodegenerative disorders. AMX0035 is an oral drug combining two compounds called sodium phenylbutyrate (PB) and tauroursodeoxycholic acid (TUDCA).

AMX0035 was tested in a phase 2/3 clinical trial called CENTAUR, which consisted of 137 participants recruited across 25 sites in the United States through the Northeast ALS (NEALS) Consortium. The trial was randomized, double-blind and placebo-controlled, and participants were assessed for a 24-week period for both safety and any effect of AMX0035 on disease progression.

All participants in the trial (active drug and placebo) were also provided an option to enroll in an open-label extension where they would receive AMX0035. This extension study will add important survival data that Amylyx intends to publish in the near future.

The clinical trial had financial support from multiple key organizations in the ALS/MND field including The ALS Association, ALS Finding a Cure and the Northeast ALS Consortium (NEALS).

Results of the trial are published in The New England Journal of Medicine [here](#)

A [press release](#) delineated the key findings of the publication as follows:

- Patients retained function longer on AMX0035 versus placebo; study achieved its primary outcome of a difference on the Revised ALS Functional Rating Scale (ALSFRS-R)
- AMX0035 is the first investigational therapy to demonstrate statistically significant benefit on this prespecified primary outcome in people with ALS since approved therapy edaravone
- AMX0035 showed numerical benefits on secondary outcomes including measures of muscle strength, breathing, and hospitalizations
- AMX0035 was generally well tolerated with similar rates of adverse events recorded in the AMX0035 and placebo groups

The publication further indicates that the effects were seen in addition to those provided by riluzole and edaravone use, though a better understanding of this additive value observation will benefit from further study. While the treatment was considered reasonably safe and tolerable, the publication also outlines that early gastrointestinal adverse events were notable and will need monitoring in future use.

An academic editorial that comments on the trial is also available [here](#). It outlines a cautious approach to interpreting the data while balancing that these results are indeed promising. The key points of the editorial are as follows:

- Well-designed, multi-center trial with “tantalizing preliminary data”
- Trial was enriched for individuals with more rapidly progressive disease, making interpretation difficult for the wider population of people living with ALS/MND



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- Secondary outcome measures were not convincingly aligned with the affect on ALSFRS-R
 - Recommendation to proceed to a confirmatory phase 3 trial with wider eligibility criteria

Additional information

a) TUDCA clinical trial

One of the compounds in AMX0035, TUDCA is also in a [phase 3 clinical trial alone](#) with 440 participants across 9 sites in Europe supported by the TRICALS initiative. In this trial, TUDCA will be tested for 18 months with twice per day oral dosing. A small phase 2 Italian clinical trial which suggested that TUDCA may positively affect disease progression over 54 weeks, was published [here](#) in 2016.

b) Sodium phenylbutyrate clinical trial

Sodium phenylbutyrate was evaluated in a small clinical trial by the NEALS consortium and published [here](#) in 2009. It was considered safe and tolerable but was not designed to determine an effect on disease progression.

Both compounds have demonstrated some success at modifying disease course in preclinical animal models.

Precautions on Self treatment

Sodium phenylbutyrate is available in some countries through prescription, approved to treat urea cycle disorders. TUDCA is widely available over the counter in many forms and as part of various supplements. It is unknown whether taking these separately will have the same affect as AMX0035, or if it's the combination that enhances the effect. Furthermore, it is unknown what the purity or active compound level of any over the counter TUDCA and sodium phenylbutyrate sources will be.

Recommendation

The SAC recommends that the Alliance communicates this as a promising set of results that are peer reviewed and achieved in a well-designed clinical trial, but also that much remains to be learned about the effect of AMX0035 in ALS/MND. The trial authors emphasize that these findings will need to be confirmed in “longer and larger trials” and the SAC encourages an approach that balances critical scientific rigour with empathy for the urgent need to have safe and effective therapies for people living with ALS/MD. Whether Amylyx seeks approval for marketing in some countries, combined with a confirmatory trial or moves forward with a larger phase 3 trial alone, the SAC will continue to update this document as our understanding of AMX0035 in ALS/MND evolves.

The SAC encourages any member organization to reach out to the company directly to enquire whether any plans exist for their country or region. The SAC will continue to keep the Alliance apprised of any



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information as it becomes known regarding next steps for Amylyx, including updating this document when open label extension/survival data is released/published in the months ahead.

With regard to self treatment regimens, the SAC strongly encourages individuals to speak with their ALS physician before considering. These promising results only pertain to compounded PB and TUDCA at the concentrations and purity tested in AMX0035.



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* SAC Member Dr. Kuldip Dave excused himself from the preparation of this note.