INTERNATIONAL ALLIANCE OF ALS/MND ASSOCIATIONS

Amylyx – AMX0035
August 2022

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). TUDCA is also commonly referred to as taurursodiol (TURSO) or ursodoxicoltaurine.

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 over a 24-week period for both safety and potential effect of AMX0035 on disease progression.

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; the 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
- 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

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. Data from this extension study was published in October 2020 in the journal Muscle & Nerve and demonstrated that individuals initially treated with AMX0035 lived an average of 6.5 months longer than those originally on placebo. This survival study strengthens the overall data. However, it is unknown at this time how the additional survival data will impact the next steps for Amylyx or the expert consensus opinion as to whether a confirmatory clinical trial is warranted. Two additional manuscripts on evaluation of survival have since been published here and here.

In 2021, Amylyx launched a 48-week, randomized placebo-controlled Phase 3 clinical trial called PHOENIX. It is expected to enroll 600 participants across 55 sites in the first collaborative effort between TRICALS (Europe) and NEALS (US). The primary outcome measure will be a joint assessment of ALSFRS-R score and survival, also known as the Combined Assesssment of Function and Survival (CAFS). Secondary outcome measures will include slow vital capacity measured both in clinic and remotely, as well as patient-reported outcomes and others. Additional details on the trial can be found here.

On November 2, 2021, Amylyx announced it had submitted a New Drug Application (NDA) to the U.S. Food and Drug Administration (FDA) for AMX0035 and on December 29 it was announced as accepted for priority review. An Expanded Access Program (EAP) for the United States was announced on March 18, 2022. On March 30 a FDA Advisory Committee was convened to discuss and vote on whether they believed the current data established a conclusion that AMX0035 was effective in ALS; the result was a 6 - 4 'no' vote. On July 5, the FDA announced it would reconvene the same Peripheral and Central Nervous System Drugs Advisory Committee (PCNDSAC) on September 7 for further discussion. Discussions will focus on the additional analyses of data from the Company's clinical studies that were determined by the FDA to constitute a major amendment to the NDA. This came soon after a June 3 announcement that the FDA decision date was pushed back to September 29 to allow more time to review the file.

On February 25, 2022, it was announced that the European Medicines Agency (EMA) agreed to review AMX0035 for potential approval.

On June 13, 2022, it was announced that Health Canada approved AMX0035 as ALBRIOZA through the Notice of Compliance with Conditions (NOC/c) pathway where one of the conditions includes confirmation of safety and efficacy in the ongoing PHOENIX Phase 3 clinical trial. As Canada became the first country anywhere in the world with regulatory approval, a regularly updated FAQ is available to help the community understand any potential for access.

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 is 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.

Summary

Given the available evidence, it is the opinion of the SAC that the initial results of the CENTAUR Phase 2 clinical trial are promising as they 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 encouraged an approach that balances critical scientific rigour with empathy for the urgent need to have safe and effective therapies for people living with ALS/MND.

Since that time Amylyx has started the Phase 3 PHOENIX clinical trial with an aim to confirm the results from Phase 2 and they have explored the possibility of approval in various regions, notably the United States, Europe and Canada. 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 information as it becomes known regarding next steps for Amylyx.

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.

SAC Members Dr. Kuldip Dave (September 2020) and Dr. Caroline Ingre (April 2021) have excused themselves from the preparation of this note.