

FDA Briefing Document

NDA# 216660

**Drug Name: AMX0035/ sodium phenylbutyrate (PB)
and taurursodiol (TURSO)**

Applicant: Amylyx Pharmaceuticals, Inc.

**Peripheral and Central Nervous System Drugs Advisory
Committee (PCNS) Meeting**

September 7, 2022

Division of Neurology 1

Office of Neuroscience

Center for Drug Evaluation and Research

DISCLAIMER STATEMENT

The attached package contains background information prepared by the Applicant and the Food and Drug Administration (FDA) for the panel members of the Advisory Committee. The background package often contains assessments and/or conclusions and recommendations written by individual FDA reviewers. Such conclusions and recommendations do not necessarily represent the final position of the individual reviewers, nor do they necessarily represent the final position of the Review Division or Office. We have brought the drug AMX3005 to this Advisory Committee in order to gain the Committee's insights and opinions, and the background package may not include all issues relevant to the final regulatory recommendation and instead is intended to focus on issues identified by the Agency for discussion by the Advisory Committee. The FDA will not issue a final determination on the issues at hand until input from the Advisory Committee process has been considered and all reviews have been finalized. The final determination may be affected by issues not discussed at the Advisory Committee meeting.

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List of Abbreviations

| Abbreviation | Definition |
|---------------------|-----------------------------------------------|
| AC | Advisory Committee |
| AD | Alzheimer's disease |
| ALS | Amyotrophic Lateral Sclerosis |
| ALSFRS-R | ALS Functional Rating Scale-Revised |
| CSF | Cerebrospinal fluid |
| ENCALS | European Network for the Cure of ALS |
| ER | Endoplasmic reticulum |
| FDA | Food and Drug Administration |
| HR | Hazard ratio |
| ITT | Intention to treat |
| MMRM | Mixed measures |
| MRI | Magnetic resonance imaging |
| NDA | New drug application |
| nFL | Neurofilament light chain |
| OLE | Open-label extension |
| OS | Overall survival |
| PET | Positron emission tomography |
| RPSFTM | Rank Preserving Structural Failure Time Model |
| SVC | Slow vital capacity |

1 INTRODUCTION

This briefing document discusses updates to the information supporting the marketing application of AMX0035 for the treatment of ALS.

1.1 Applicant Proposed Indication

Proposed indication: AMX0035 is indicated for the treatment of amyotrophic lateral sclerosis (ALS).

1.2 Purpose of the Meeting

We are reconvening the committee to continue discussion of the application in the context of the additional analyses and data submitted by the Applicant.

1.3 Draft Points to Consider

Consider the strength of the currently available data regarding effectiveness, to include the new information submitted and the information presented at the prior AC meeting, in the context of the unmet need in amyotrophic lateral sclerosis (ALS), the status of the ongoing Phase 3 trial, and the seriousness of ALS.

2 BACKGROUND

The Peripheral and Central Nervous System (PCNS) Drugs Advisory Committee (AC) met on March 30, 2002, to discuss whether the data submitted by the Applicant is adequate to establish the effectiveness for AMX0035 in the treatment of amyotrophic lateral sclerosis (ALS). At this prior meeting, following discussion, four committee members voted “Yes” (indicating that they felt the data supported the effectiveness of AMX0035 for ALS), and six members voted “No” (indicating that they did not feel that the data supported the effectiveness of AMX0035 in ALS).

Following the AC meeting, the Applicant submitted additional analyses of the survival data from the CENTAUR study and its open-label extension, along with biomarker results from a recently completed Phase 2 study of AMX0035 in Alzheimer’s disease. The Applicant informed the Agency that the data and analyses in the new submission were intended to contribute to the confirmatory evidence to accompany the primary result of the CENTAUR study. As discussed with the committee previously, one

successful study accompanied by confirmatory evidence may be an acceptable approach to the provision of the substantial evidence of effectiveness required for marketing approval. These additional analyses and new data constituted a major amendment to the application, which extended the review timeline by 3 months to allow for adequate consideration of this new information.

These analyses contained no new data from the CENTAUR study or its open-label extension; the submission consisted of new analyses of previously submitted survival data. Additionally, the Applicant provided biomarker data from the Alzheimer's disease study to show the effects of AMX0035 on markers of neurodegeneration in another neurodegenerative disease.

We are reconvening the committee to continue discussion of the application in the context of the additional analyses and data submitted by the Applicant. Recognizing the substantial unmet medical need in ALS, as exists for so many of the devastating neurological diseases for which treatments are desperately needed, we feel that it is important that the committee is afforded the opportunity to consider this new information, along with the information presented at the prior AC meeting, in that context.

2.1 Summary of PCNS AC meeting on March 30, 2022

Following is a brief summary of the presentations and discussions from the previous AC meeting on March 30, 2022.¹

To support a finding of substantial evidence of effectiveness, the Applicant submitted data from a single double-blind, placebo-controlled Phase 2 Study (AMX3500, also titled CENTAUR) in 137 patients with ALS. The Applicant reported a statistically significant result on the primary endpoint of the slope of the ALS Functional Rating Scale-Revised (ALSFRRS-R) change at 24 weeks (2.32-point difference at 24 weeks, $p=0.034$). The ALSFRRS-R is an acceptable functional endpoint for a clinical trial in ALS; however, FDA raised concerns with the statistical analysis methodology which did not appropriately account for deaths that occurred during the study. Additionally, FDA noted that the prespecified statistical result was not exceptionally persuasive and there were analytical and interpretative issues associated with its consideration. FDA expressed concerns that the data may not be adequate to serve as a single study capable of independently providing substantial evidence of effectiveness.

¹ Meeting materials and transcripts from the March 30, 2022, PCNS advisory committee meeting are available online.

<https://www.fda.gov/advisory-committees/peripheral-and-central-nervous-system-drugs-advisory-committee/updated-meeting-time-and-open-public-hearing-time-march-30-2022-meeting-peripheral-and-central#event-materials>

The Applicant also submitted data from an open-label extension study (AMX3500OLE) and reported findings of a survival benefit in patients who initially received AMX0035 compared to those patients who originally received placebo in the CENTAUR study. FDA noted concerns about the interpretability of the survival benefit given the large number of dropouts in the open-label extension period and baseline imbalances between the populations.

FDA had advised the Applicant prior to submission of its marketing application that an additional Phase 3 study appeared necessary to confirm the findings discussed above. The Applicant has an ongoing Phase 3 study in 600 patients with ALS worldwide. The study has currently enrolled over 50% of the proposed study population and is expected to complete in late 2023 to early 2024.

The committee was asked to vote on the following question:

“Do the data from the single randomized, controlled trial and the open-label extension study establish a conclusion that sodium phenylbutyrate/taurursodiol is effective in the treatment of patients with amyotrophic lateral sclerosis (ALS)?”

Four members voted “Yes” and six members voted “No”. There were no abstentions. All members who voted expressed similar sentiments that the decision was difficult.

3 MAJOR AMENDMENT

3.1 New information submitted as confirmatory evidence

The Applicant acknowledged limitations to the CENTAUR study that may impact its ability to stand alone as a single study to demonstrate substantial evidence of effectiveness and submitted the following information as potential confirmatory evidence to support the treatment benefit seen in the CENTAUR study.

As previously noted, CENTAUR was a 137 participant, randomized, placebo-controlled, double-blind study in patients with ALS that met its prespecified primary outcome, a statistically significant change on the slope of the ALSFRS-R at 24 weeks (2.32-point difference at 24 weeks, $p=0.034$). The Applicant has provided additional analyses as confirmatory evidence in an effort to support the findings in the CENTAUR study.

3.2 Responder Analysis based on the ALSFRS-R of the proportion of patients in the original trial who had an unusually strong response

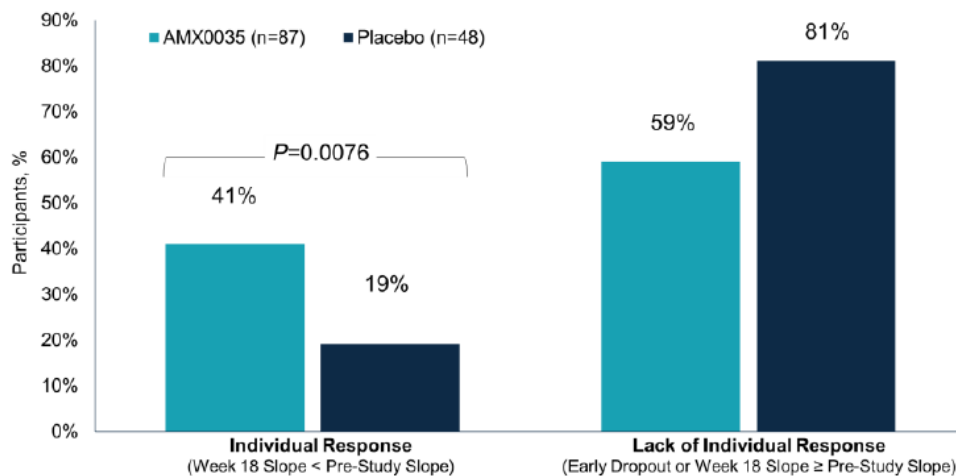
The first additional analysis is an individual responder analysis that uses participants as their own controls and compares the response rate in the AMX0035 group to the response rate in the placebo group. The Applicant conducted this post hoc analysis to

compare the progression rate of individual subjects during the study to their own progression rates prior to entering the study as independent confirmatory evidence of individual effect of the treatment. This individual responder analysis uses participants as their own controls, and the Applicant believes that it may be less affected by any baseline differences between groups.

To conduct this analysis, the Applicant calculated the number of patients within each study arm that had a slower rate of progression during the study at Week 18 compared to their pre-baseline progression rate (pre-study slope). To calculate the pre-study slope, the Applicant calculated the points lost on ALSFRS-R divided by months since ALS symptom onset at the baseline visit. Responders were defined as those patients whose actual rate of change during the study (at Week 18) was less than their own pre-baseline progression rate. Non-responders were defined as those whose actual rate of progression was greater than or equal to their own pre-baseline progression rate, patients who dropped out of the study prior to Week 12, and patients who died prior to Week 18. The Applicant states that Week 18 data was chosen for this analysis to minimize the extent of missing data due to patient drop-out but is also a time point at which response to treatment would be evident.

The Applicant reports that an individual response was observed in a greater proportion of patients receiving AMX0035 (41%; 95% CI 31-52%) vs placebo (19%; 95% CI: 8-30%), odds ratio 3.06, $p=0.0076$ (Figure 1).

Figure 1: CENTAUR ALSFRS-R Individual Response by Treatment Group (mITT population)



FDA Position:

This post hoc analysis is highly correlated with the primary analysis. Both change from baseline slope and pre-study slope were used in the primary analysis; thus, this is not independent data. Therefore, it does not appear that this data can be considered independent confirmatory evidence as it uses the same data as the primary analysis. Also, notwithstanding the Applicant's explanation, it is unclear why the Applicant has chosen to compare the treatment effect at Week 18, rather than Week 24 (the primary analysis endpoint). We note that the effect size on the primary endpoint was larger at Week 18 than Week 24.

Additionally, the Applicant claims that using participants as their own control may provide independent evidence of effectiveness; however, this analysis doesn't completely use participants as their own controls. The analysis is still a comparison between groups, comparing the response rate of patients receiving treatment to the response rate of patients receiving placebo. A true within-patient analysis that uses patients as their own control should calculate a treatment difference for each patient enrolled in the study; this is not possible for patients assigned placebo in this study design, and thus, is not an independent analysis from the primary analysis. Additional concerns with this analysis include:

- The pre-study slope was not directly measured and was calculated based on retrospectively collected data.
 - o The variability of the change in slope may not be constant, because "delFS" depends on time from symptom onset, which varies widely across patients and the mean time from symptom onset of 59 weeks is significantly longer than the double-blind follow-up of 18 weeks considered in this analysis.
 - o Pre-randomization slope is based on a baseline measurement/presumed score of 48 (normal) at disease onset. It is unlikely that patients would have a maximum score at the time of diagnosis because they would have signs and symptoms of ALS that prompted the work-up and subsequent diagnosis.
 - o Linearity seems questionable for the pre-randomization slope because this slope is calculated over a period of up to 608 days, which is much longer than the 24 weeks of the primary efficacy study, for which the prior review showed linearity may not hold.
 - o There is no way to check linearity of the pre-randomization slope.
- There is post-baseline starting of ALS medications, more in the drug arm, which could confound this analysis.

Therefore, these data appear limited in their ability to provide independent substantiation for the observed effect on [the primary endpoint.

3.3 Randomized, long-term overall survival (OS) information that highlight a critical and complementary finding to the primary outcome and analyses

The Applicant contends that survival analyses from CENTAUR and the OLE can also serve as confirmatory evidence for the effectiveness of AMX0035 in ALS, given that death is an objective assessment.

The Applicant again presented the ITT Overall Survival (OS) in the OLE as of March 1, 2021, the specified last day of the open-label treatment extension. This analysis is the same analysis previously submitted to the NDA and discussed with the committee.

CENTAUR included a double-blind treatment period for 24 weeks. After that, all patients were given the option to enroll in an open-label, long-term extension study to evaluate long-term safety and efficacy outcomes, including survival. The Applicant notes that OS is not affected by drop-outs, since vital status was able to be collected in all randomized patients but one (136 out of 137 patients originally enrolled in CENTAUR). The Applicant also reports that patients and investigators remained blinded to the assigned treatment in the randomized phase throughout the open-label extension study.

For ITT participants, there was a nominally significant overall survival benefit (HR=0.64) with longer median OS (23.5 months) observed in patients randomized to AMX0035 than the median OS of patients randomized to placebo (18.7 months) for a difference of 4.8 months. This analysis was reported and reviewed during the initial NDA submission and discussed at the prior AC meeting.

However, the Applicant now indicates that because the majority of placebo patients (71%) crossed over into the OLE and received AMX0035, the ITT overall survival does not account for treatment crossover and may underestimate the survival benefit of the drug.

Therefore, two post hoc sensitivity analyses are provided to address this potential crossover effect and are presented below.

- 1) Using Natural History data to estimate benchmark survival time as the control
- 2) Using Rank Preserving Structural Failure Time Model (RPSFTM)

1) Survival prediction algorithm created from natural history data

The first sensitivity analysis predicts overall survival time from baseline prognostic factors created using data from more than 10,000 people with ALS from 14 specialized ALS centers across Europe (ENCALS survival prediction model). The Applicant worked with the originators of this survival model to

produce survival predictions for each individual participant in CENTAUR. They calculated a Risk Profile for each subject and translated it to absolute survival probabilities based on the ENCALS survival prediction model.

Per the Applicant, the AMX0035 and placebo groups had similar risk profiles and similar predicted survival at baseline, suggesting that the groups were well balanced at baseline on the commonly known prognostic factors.

The Applicant's analysis shows that the median OS in the ITT AMX0035 treatment arm (N=89, OS=23.5 months) showed a prolongation of median OS of 9.9 months versus the ENCALS predicted treatment naïve median survival (13.6 months model predicted survival, $p < 0.0001$). This analysis compares the treatment arm with a treatment naïve benchmark so does not have the concern regarding crossover of the placebo group.

FDA Position:

There are a variety of concerns about the reliability of this analysis. Notably, this is a non-randomized comparison to an external control that is subject to potential confounding due to differences between the AMX0035-treated patients and the external controls in unmeasured prognostic factors, measured prognostic factors not accurately measured or captured by the survival prediction model, and/or supportive care/interventions. FDA also notes that patients in the natural history database were not in a clinical trial which could also lead to differences between the groups. Furthermore, there was no pre-specified protocol and/or analysis plan for this comparison and post hoc analyses are challenging to interpret. Finally, we note that the same multiplicity issue exists here as with the ITT mortality analysis based on comparing randomized groups in that death alone was not a pre-specified primary or secondary endpoint in the double-blind period or the OLE.

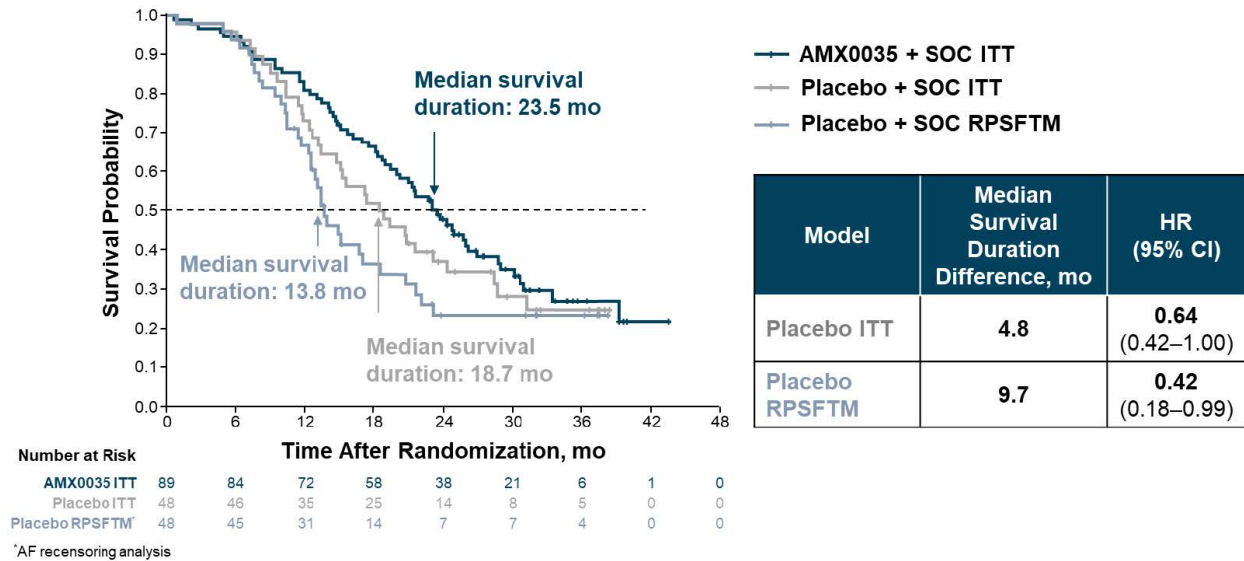
2) Rank Preserving Structural Failure Time Model (RPSFTM) to account for treatment crossover

The Applicant states that other fields, such as oncology, have utilized placebo crossover design to maintain ethical clinical trial designs, while also providing estimation of survival benefit of treatment. One of these approaches to estimate survival benefit is the rank-preserving structural failure time model (RPSFTM), which controls for the effect of crossover in OS results if the associated untestable assumptions hold. The RPSFTM provides an estimate of the OS time for the placebo group, had treatment switching not occurred.

The Applicant used such a model to analyze the CENTAUR OLE data and demonstrated that the estimated median survival benefit for AMX0035, as of March 1, 2021, was 9.7 months, compared to the 4.8 month OS benefit seen in

the original NDA analysis. The estimated hazards ratio (HR) was 0.42 (0.18, 0.99) compared to the original 0.64 (0.42, 1.00). These results were published in *Muscle & Nerve*² and are presented below in Figure 2.

Figure 2: Rank Preserving Structural Failure Time Model Results



FDA Position:

The presented RPSFTM analysis is not independent data and is simply a new method for analyzing the same survival data presented in the original NDA submission. The Applicant has conducted this new analysis to attempt to estimate what survival would have been in patients assigned to placebo had they never entered the OLE. This can only be done with strong, untestable assumptions. Furthermore, there were no prespecified analyses to adjust the placebo arm for switching to AMX0035 in the OLE in the placebo vs. AMX0035 comparison, i.e., this is a post hoc analysis. Such switching was mandated for continuing placebo completers by study design, which reduces the ability to answer the question of a possible survival benefit of the original AMX0035 arm compared to a hypothetical, unswitched placebo arm. The analysis also suffers from the same interpretability challenges as the ITT analysis based on the randomized groups, such as multiplicity issues due to the exploratory nature of the death alone analysis. Despite all of these limitations, it is notable that while the estimated effect from this analysis is slightly larger, the confidence interval is

² Supplementary Appendix to Paganoni S, Watkins C, Cawson M, et. al. Survival analyses from the CENTAUR trial in amyotrophic lateral sclerosis: Evaluating the impact of treatment crossover on outcomes. *Muscle Nerve* 2022 May 4. doi: 10.1002/mus.27569. Epub ahead of print.

wider and the p-value is the same as from the ITT analysis based on the randomized groups.

The following expands on the concerns about the reliability of the analysis and its heavy reliance on strong unverifiable assumptions. The new analysis comparison is counterfactual, i.e., it relies on assumptions about what the survival of patients assigned to placebo would have been had they never switched to AMX0035 in the OLE. These assumptions and the analysis are questionable because most eligible placebo patients switched to AMX0035 by design, and the ineligible placebo group (those patients who did not complete the double-blind period) is not a random subset. In fact, the placebo patients who dropped out during the double-blind period have a worse baseline average ALSFRS-R than the placebo completers (i.e., eligible patients for switching). Within the placebo arm (n=48), the mean baseline ALSFRS-R is 4.5 points higher for completers (37.6, n=38) than for dropouts (33.1, n=10) and there is a similar difference in baseline ALSFRS-R between double-blind period AMX0035 dropouts (also not eligible to continue into the OLE) and AMX0035 completers. The Latimer et al.³ paper (a reference cited by the Paganoni article) suggests that, based on a simulation study, 1) the analysis with re-censoring is biased in favor of the treatment arm and should therefore be accompanied by an analysis without re-censoring (however the applicant stated that there was no viable solution for this data for the RPSFTM model without re-censoring), and 2) the bias of the re-censoring analysis increases with the proportion switching, which is very high for the placebo arm in this trial.

Furthermore, most of the following best practices for the RPSFTM analysis were not implemented in this situation:

- Carefully consider whether to include switch in trial design; it is preferable not to include this from a data interpretation perspective.
- Include the planned method to handle switching up front in protocol and analysis plan.
- Consider contemporaneous collection of data on treatment without switch outside the trial, in a comparable setting, to provide external validation.
- Consider sensitivity analyses using other methods.

The following is a summary of limitations of the RPSFTM method:

³ NR Latimer, IR White, KR Abrams and U Siebert. Causal inference for long-term survival in randomised trials with treatment switching: Should re-censoring be applied when estimating counterfactual survival times? *Statistical Methods in Medical Research* 2019, Vol. 28(8) 2475–2493.

- The assumption that the treatment effect on survival time is proportional to time on drug regardless of drug start time may not be realistic in many diseases, especially in degenerative conditions such as ALS.
- Simulations show that this method can lead to large biases.
- Results can be unstable if the amount of treatment (duration) is similar in both arms (this might possibly explain the lack of a solution for this data for the version of this model without re-censoring).

In conclusion, FDA does not find these data sufficiently independent or persuasive to serve as independent confirmatory evidence of effectiveness.

3.4 Mechanistic Evidence for Impact on Neurodegeneration and Neuroinflammation in CSF of a Related Disease Population

The Applicant conducted a randomized, placebo-controlled study (PEGASUS) in patients with clinical Alzheimer’s disease (AD) or mild cognitive impairment, accompanied by a variety of biomarkers supporting AD pathology (i.e., amyloid PET, cerebrospinal fluid (CSF) AD biomarkers, fluorodeoxyglucose-PET, or volumetric MRI). The Applicant hypothesizes that AMX0035 may be able to reduce neuronal degeneration by targeting endoplasmic reticulum (ER) stress and mitochondrial dysfunction. According to the Applicant, phenylbutyrate and taurursodiol were both reported to show benefit on amyloid burden in mouse models of AD. The Applicant notes that ER stress and mitochondrial dysfunction may be implicated in both AD and ALS pathogenesis.

The PEGASUS study enrolled 95 patients, with 51 patients on AMX0035, and 44 patients on placebo. Overall, 80% of AMX0035 patients and 96% of placebo patients completed the study. Patients received AMX0035 or placebo twice daily for 24 weeks. The study assessed 18 CSF biomarkers that were felt to be core AD biomarkers or targets of the presumed mechanism of action of AMX0035. These biomarkers were prospectively specified as exploratory endpoints. Results of the change from baseline at 24 weeks in the selected CSF biomarkers are reported in Table 1 below.

Table 1: Change from Baseline in CSF Biomarkers after 24 Weeks in the PEGASUS study

| Biomarker | AMX0035 | Placebo | LSMEAN Difference (95% CI) | p-value |
|-----------------------------|---------|---------|----------------------------|---------|
| Neurodegeneration | | | | |
| Total Tau*(pg/mL) | -64.93 | 8.82 | -73.74 (-106.84, -40.65) | <0.0001 |
| Phosphorylated Tau* (pg/mL) | -14.63 | -0.27 | -14.36 (-21.51, -7.21) | 0.0002 |
| FABP3 (pg/mL) | -344.62 | 102.90 | -447.52 (-684.59, -210.45) | 0.0004 |

| | | | | |
|------------------------------------------|-----------|---------|---------------------------------|--------|
| NfL (pg/mL) | 169.48 | 63.61 | 105.87 (-119.74, 331.47) | 0.35 |
| Synaptic Function | | | | |
| Neurogranin (pg/mL) | -81.19 | -8.34 | -72.85 (-220.82, -34.89) | 0.0003 |
| Inflammation | | | | |
| YKL-40 (pg/mL) | -14635.39 | 1507.88 | -16143.27 (-26995.89, -5290.65) | 0.004 |
| IL-15 (pg/mL) | -0.02 | 0.25 | -0.28 (-0.49, -0.06) | 0.01 |
| IL-6 (pg/mL) | 644.38 | 565.93 | 78.45 (-1042.5, 1199.40) | 0.89 |
| IL-8 (pg/mL) | 1.54 | 1.17 | 0.37 (-4.37, 5.11) | 0.88 |
| GFAP (pg/mL) | 821.68 | 488.15 | 333.53 (-2080.17, 2747.22) | 0.78 |
| MCP-1 (pg/mL) | -1.97 | -0.79 | -1.18 (-21.15, 18.79) | 0.91 |
| Core AD Pathology | | | | |
| AB ₄₂ /AB ₄₀ ratio | 0.0039 | -0.0051 | 0.0090 (0.0029, 0.0151) | 0.005 |
| AB ₄₂ (pg/mL) | -8.09 | -41.46 | 33.37 (-38.37, 105.11) | 0.36 |
| AB ₄₀ (pg/mL) | -752.7 | -754.81 | 2.11 (-1007.67, 1011.88) | 1.0 |
| Metabolism/Oxidative Stress | | | | |
| 8-OHdG (pg/mL) | 0.31 | -0.13 | 0.44 (0.13, 0.74) | 0.006 |
| 24=OHC (pg/mL) | -0.20 | -0.07 | -0.13 (-0.67, 0.41) | 0.63 |
| Leptin (pg/mL) | 0.45 | 4.53 | -4.09 (-25.71, 17.54) | 0.71 |
| sIR (pg/mL) | -0.04 | -0.19 | 0.15 (-0.25, 0.55) | 0.47 |
| Neurovascular | | | | |
| MMP-10 (pg/mL) | -3.13 | -0.92 | -2.21 (-8.5, 4.1) | 0.48 |

* Tau and Phosphorylated Tau may also be considered core AD pathology; Source: Applicant Submission Table 3

Applicant conclusion:

The Applicant indicates that the improvement in select CSF biomarkers supports the mechanistic activity of AMX0035 in the central nervous system (CNS). AMX0035 lowered levels of CSF total tau, p-tau 181, neurogranin, and YKL-40, and raised the ratio of A β ₄₂/A β ₄₀, markers of neurodegeneration that are felt to be relevant to AD pathology. The Applicant believes that these biomarkers may provide additional insight into the role of AMX0035 in patients with ALS, because CSF total tau, p-tau 181, and YKL-40 have also been shown to be elevated in patients with ALS.

FDA position:

The reported changes in a select number of the studied biomarkers may be suggestive of pharmacodynamic activity of AMX0035 in the CNS in patients with Alzheimer's disease, but there is no clear or consistent relationship between the biomarkers that had nominally significant findings and the ones that did not to suggest a true treatment benefit on nervous system inflammation or neuronal degeneration. Neurofilament light chain (nFL), a frequently measured biomarker of neuronal degeneration, did not show a nominally significant change during the 24-week study.

Additionally, as the underlying pathophysiology of AD and ALS are different, the relevance of a change in tau, phosphorylated tau, YKL-40, or A β ₄₂/A β ₄₀ ratio in AD patients to patients with ALS is unknown. It is unclear if these findings, even if they were demonstrated to be indicative of benefit in AD, would be generalizable to ALS. Additionally, the 18 biomarkers were assessed as exploratory endpoints and thus

were not adjusted for multiplicity; therefore, the interpretation of the p-values is limited. The submitted biomarker data are not clear evidence of a CNS effect or a potential for clinical benefit in patients with ALS.

4 ADDITIONAL REGULATORY BACKGROUND

As noted above, there is a substantial unmet medical need in ALS, as exists for so many of the devastating neurological diseases for which treatments are desperately needed, with the ability to apply regulatory flexibility in the face of this demonstrated need. As described in the 2019 FDA draft guidance on “Demonstrating Substantial Evidence of Effectiveness for Human Drug and Biological Products”:⁴ “In all cases, FDA must reach the conclusion that there is substantial evidence of effectiveness to approve a drug; however, the degree of certainty supporting such a conclusion may differ, depending on clinical circumstances (e.g., severity and rarity of the disease and unmet medical need).”

The following information is provided as additional regulatory context for the committee members to inform panel discussions.

4.1 Regulatory pathways to approval

Substantial Evidence of Effectiveness

To approve a drug, substantial evidence of effectiveness must be provided by the Applicant. This standard must be met for all diseases, ranging from common, mild, non-life-threatening conditions with limited morbidity and abundant available treatments to serious, life-threatening, and/or fatal diseases with limited available treatments. In the neurological space, essentially all diseases fall into some aspect of the latter category and demand the application of regulatory and scientific consideration and flexibility appropriate to the context of the disease for which a given treatment is being developed, along with a contextual consideration of the issues associated with that treatment. Although two adequate and well-controlled clinical investigations are the typical standard for generating substantial evidence of effectiveness in many disease settings, there are scenarios in which a single trial can be used to establish effectiveness, either with or without additional confirmatory evidence. As described in FDA’s 1998 guidance, “Providing Clinical Evidence of Effectiveness for Human Drug and Biological Products”⁵ and reiterated in the 2019 draft FDA Effectiveness Guidance,

⁴ <https://www.fda.gov/regulatory-information/search-fda-guidance-documents/demonstrating-substantial-evidence-effectiveness-human-drug-and-biological-products>. When finalized, this guidance will represent the current thinking of the FDA on this topic.

⁵ <https://www.fda.gov/regulatory-information/search-fda-guidance-documents/providing-clinical-evidence-effectiveness-human-drug-and-biological-products>

in the absence of confirmatory evidence, reliance on a single trial to establish effectiveness should generally be limited to situations in which the trial has demonstrated a clinically meaningful and statistically very persuasive effect on mortality, severe or irreversible morbidity, or prevention of a disease with potentially serious outcome, and confirmation of the result in a second trial would be impracticable or unethical. Essentially, we are able to rely on the evidence from a single trial in isolation when it provides evidence that is similarly persuasive to that which might result from two separate trials taken together. As we discussed with the committee previously, it appears that the primary evidence provided by the placebo-controlled CENTAUR study, in absolute isolation, is undoubtedly promising but does not appear independently persuasive.

Under certain circumstances, FDA can also conclude that one adequate and well-controlled clinical investigation plus confirmatory evidence is sufficient to establish effectiveness.

Factors that FDA may consider relevant to such a situation are described in the aforementioned 2019 guidance, and include:

- The persuasiveness of the single trial
- The robustness of the confirmatory evidence
- The seriousness of the disease and whether there is an unmet need
- The size of the patient population
- Whether it is ethical and practicable to conduct more than one adequate and well-controlled clinical investigation

As further described in the guidance, examples of confirmatory evidence may include:

- Data from adequate and well-controlled clinical studies that demonstrate the effectiveness of the drug in a closely related approved indication
- Data that provide strong mechanistic support of the drug in the pathophysiology of the disease
- Data from a well-documented natural history of the disease can potentially reinforce very persuasive and compelling results from a single AWC study.
- Scientific knowledge about the effectiveness of other drugs in the same pharmacological class

The same statutory standards for effectiveness apply to all new drugs, including drugs developed for ALS. However, FDA has also long stressed the appropriateness of exercising regulatory flexibility in applying the statutory standards to drugs for serious disease with unmet medical needs, while preserving appropriate assurance of safety and effectiveness. (21 CFR 312.80 subpart E, Drugs Intended to Treat Life-Threatening

and Severely Debilitating Illnesses). Whether one trial, one trial plus confirmatory evidence, or two trials, consideration of the character and persuasiveness of the evidence must take into account the nature of the disease under consideration and the associated unmet medical need. In the neurological space, we will unfailingly consider the evidence, whatever its quantity, in that context.

Accelerated approval

Often, when discussing substantial evidence of effectiveness, we are discussing evidence based on direct assessment of clinical benefit, and such substantial evidence may result in a traditional approval. Accelerated approval is a particular type of approval that FDA may grant for a product for a serious or life-threatening disease or condition upon a determination that the product has an effect on an endpoint that is not itself a direct measure of the clinical benefit of interest but is instead reasonably likely to predict that clinical benefit, taking into account the severity, rarity, or prevalence of the condition and the availability or lack of alternative treatments.

Concerning accelerated approval, it is crucial to recognize that the evidentiary standards for effectiveness are not lower for endpoints used to support accelerated approval than those used for traditional approval. Substantial evidence of an effect on those endpoints must be demonstrated. As we discussed with the committee previously, substantial evidence comes from adequate and well controlled investigations and is evidence that the drug will have the effect it purports or is represented to have in labeling. Accelerated approval concerns the character of the endpoints, not the strength of the results on those endpoints. An effect on an endpoint supporting accelerated approval must be an effect on an endpoint that in its character is reasonably likely to predict clinical benefit and, in its persuasiveness, provides substantial evidence of effectiveness from adequate and well controlled trials, just as substantial evidence of effectiveness on a clinically meaningful endpoint from adequate and well controlled trials supports traditional approval.

In the case of AMX0035 for ALS, we do not have data for an effect of AMX0035 on an endpoint that is reasonably likely to predict clinical benefit for ALS. The ALSFRS-R and survival are direct measures of clinical benefit and are acceptable endpoints to support traditional approval; therefore, if the Applicant provided data for these endpoints that met the substantial evidence requirements, the Agency would be able to grant a traditional approval.

It is also worth noting that some other countries have “conditional approval” marketing authorization pathways that allow for an approval of a product that does not meet the evidentiary standards for effectiveness required for “full” approval in those countries. This pathway may often be confused for the “accelerated approval” pathway in the US; however, there are distinct differences. Although both pathways are intended to expedite the availability of therapies that address an unmet need, the “conditional” pathway may allow for the marketing authorization for products for which the benefit-risk

of the medicine is positive, the benefit of immediate availability of the drug to patients is greater than the risk inherent in the fact that additional data are still required, and it is likely that the Applicant will be able to provide comprehensive data after marketing authorization is granted.⁶ However, in contrast to the accelerated approval pathway in the US, the “conditional” pathway does not have a requirement for substantial evidence of effectiveness.

In this regard, it is important for the committee to be aware of and note the recent approval of AMX0035 in Canada, using one of these “conditional approval” pathways, the Health Canada regulatory authority known as “Notice of Compliance with Conditions (NOC/c)”. This form of market authorization is granted to a product on the basis of promising evidence of clinical effectiveness. “Promising clinical evidence” is explained by Health Canada to be evidence based on well-controlled and well-conducted clinical trials establishing that the drug product has an effect on a surrogate or clinical endpoint that is reasonably likely to predict clinical benefit.⁷ It is thus similar in some ways to FDA’s accelerated approval pathway but relies on promising evidence rather than substantial evidence.

4.2 Unmet medical need

There are currently two approved products for ALS in the US, riluzole and edaravone. Although these drugs have demonstrated benefits for ALS, the disease remains progressive and fatal despite these available therapies. There is an urgent unmet medical need for new treatments for individuals with ALS. This unmet need provides important context when considering the evidence supporting the AMX0035 application.

4.3 Regulatory flexibility

Our regulations allow for regulatory flexibility to expedite the development, evaluation, and marketing of new therapies intended to treat persons with life-threatening and severely debilitating illnesses, especially where no satisfactory alternative therapy exists. As stated in 21 CFR 312.80 Subpart E Drugs Intended to Treat Life-Threatening and Severely-Debilitating Illnesses:

“The Food and Drug Administration (FDA) has determined that it is appropriate to exercise the broadest flexibility in applying the statutory standards, while preserving appropriate guarantees for safety and effectiveness. These procedures reflect the

⁶ <https://www.ema.europa.eu/en/human-regulatory/marketing-authorisation/conditional-marketing-authorisation>

⁷ <https://www.canada.ca/en/health-canada/services/drugs-health-products/drug-products/applications-submissions/guidance-documents/notice-compliance-conditions.html>

recognition that physicians and patients are generally willing to accept greater risks or side effects from products that treat life-threatening and severely debilitating illnesses, than they would accept from products that treat less serious illnesses. These procedures also reflect the recognition that the benefits of the drug need to be evaluated in light of the severity of the disease being treated.”

The 2019 FDA draft guidance, “Demonstrating Substantial Evidence of Effectiveness for Human Drug and Biological Products”, discusses clinical circumstances where additional flexibility may be warranted, such as when a disease is rare or the disease is life-threatening or severely debilitating with an unmet medical need.

The guidance states that, “in certain settings, a somewhat greater risk (compared to placebo-controlled or other randomized superiority trials) of false positive conclusions – and therefore less certainty about effectiveness – may be acceptable, when balanced against the risk of rejecting or delaying the marketing of an effective therapy, (...) for an unmet medical need.”

The guidance provides examples of the use of regulatory flexibility in consideration of alternate trial designs to the standard randomized, double-blind, placebo-controlled study and the use of surrogate or intermediate clinical endpoints under the accelerated approval pathway. Additionally, the guidance states when flexibility may be considered on the p-value:

“A typical criterion for concluding that a trial is positive (showed an effect) is a p value of < 0.05 (two sided). A lower p value, for example, would often be expected for reliance on a single trial. For a serious disease with no available therapy or a rare disease where sample size might be limited, as discussed further below, a somewhat higher p value – if prespecified and appropriately justified – might be acceptable.”

Regarding the number of trials considered sufficient to establish effectiveness, the guidance states that a single trial may be sufficient “when a large multicenter trial has demonstrated a clinically meaningful and statistically very persuasive effect on mortality, irreversible morbidity, or prevention of a disease with potentially serious outcome, a second trial would be impracticable or unethical.” For rare diseases the guidance notes that, “a second trial may be infeasible in certain rare disease settings where the limited patient populations preclude the conduct of a second trial. In these cases, the substantial evidence of effectiveness would typically be provided by a single trial plus confirmatory evidence.”

4.4 History of regulatory flexibility in ALS

There are two FDA-approved treatments for ALS, riluzole and edaravone. Both approvals demonstrate the Agency’s history of regulatory flexibility in ALS.

Riluzole (Rilutek) was approved for ALS in 1995. The exact mechanism by which riluzole exerts its therapeutic effects in patients with ALS is unknown, although it is purported in the literature to modulate the neurotransmitter glutamate.

The approval of riluzole for the treatment of ALS was based on two adequate and well-controlled trials that assessed survival. In both studies, riluzole did not show a statistically significant difference using the pre-specified statistical analysis method ($p=0.12$ and 0.076). The Agency felt that an alternative test was a more appropriate statistical analysis method for these trials. Using this methodology, both studies were found to demonstrate statistically significant effects on survival ($p=0.05$ for both studies). These post hoc results using an alternative test in the two studies that resulted in an exploratory finding of nominal significance was found to meet the substantial evidence of effectiveness standard for riluzole in ALS.

The intravenous (IV) formulation of edaravone (Radicava) was approved for the treatment of ALS in 2017, and an oral formulation (Radicava ORS) was approved for ALS in 2022. The exact mechanism by which edaravone exerts its therapeutic effects in patients with ALS is unknown, although it is purported in the literature to have an antioxidant effect.

The approval of edaravone for the treatment of ALS was based on a single 6-month randomized, double-blind, placebo-controlled trial conducted in 137 Japanese patients (randomized 1:1) with ALS who were living independently.

The study demonstrated a statistically significant difference of 2.5 units (95% confidence interval 1.0, 4.0; $p=0.013$) in decline of the ALSFRS-R. The results were corroborated by multiple sensitivity analyses conducted by FDA (MMRM analysis $p=0.0003$, Wilcoxon joint rank $p=0.0009$). Results of several secondary endpoints trended favorably. FDA noted that the study had characteristics that made it appropriate, as a single study, to provide substantial evidence of effectiveness. Some of these characteristics included: a multicenter study in which no single site contributed an unusually large fraction of the patients and no single site was disproportionately responsible for the treatment effect; consistency across subsets of study participants; persuasive results with strong p-values.

Although every drug development program is distinct and must be considered individually, this history of the application of regulatory flexibility in ALS is a relevant precedent for both ALS and other neurological diseases and should be taken into account when considering the evidence supporting the AMX0035 application.

4.5 Ongoing Phase 3 trial

Study A35-004 (PHOENIX) (NCT05021536) is a Phase 3, randomized, placebo-controlled trial of AMX0035 in patients with ALS. The primary objective of the trial will be to assess AMX0035 compared to placebo on the change from baseline of ALSFRS-R

and survival over 48 weeks. The study also includes assessments of respiratory function (slow vital capacity (SVC)), several patient-reported outcomes, and ventilation-free survival rates. The study will enroll approximately 600 subjects at over 70 sites in the US and Europe. The trial is expected to complete in late 2023 or early 2024 with results available shortly thereafter.

This places the Agency in a challenging situation of potentially making a regulatory decision that may not be subsequently aligned with the results of the ongoing study.

4.6 Expanded Access

The Applicant has an expanded access program available in the United States (US), Study A35-006, to allow for access for AMX0035 for eligible adults with ALS with symptoms for at least 3 years and who are not eligible to participate in clinical trials.

Details regarding the US expanded access program are available on the applicant's website "US Early Access Program" and in clinicaltrials.gov (ClinicalTrials.gov Identifier: NCT05286372).