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September 23, 2022

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Commissioner
Food and Drug Administration
U.S. Department of Health and Human Services
10903 New Hampshire Avenue
Silver Spring, MD 20993

Patrizia Cavazzoni, M.D.
Director
Center for Drug Evaluation and Research
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Re: NDA# 216660 for AMX0035, Sodium Phenylbutyrate and Taurursodiol (Amylyx Pharmaceuticals) for Treatment of Amyotrophic Lateral Sclerosis

Dear Drs. Califf and Cavazzoni:

Public Citizen, a consumer advocacy organization with more than 500,000 members and supporters nationwide, strongly urges the Food and Drug Administration (FDA) to not approve AMX0035 (sodium phenylbutyrate and taurursodiol) for treatment of amyotrophic lateral sclerosis [ALS]) at this time because the data from the single phase 2 clinical trial (CENTAUR) and its open-label extension study remain inconclusive for several reasons including the studies' design, implementation, and the marginal effects observed.

As we noted in our testimony during the open public hearing at the first meeting of the FDA's Peripheral and Central Nervous System Drugs Advisory Committee (PCNS) regarding AMX0035 on March 30, 2022, a 2017 study by your agency described 22 examples of favorable phase 2 clinical trial results that were not confirmed in subsequent phase 3 clinical trials with respect to effectiveness (14 medical products), safety (one medical product), or both effectiveness and safety (seven medical products).[1]

Regarding the new drug application for AMX0035 (NDA# 216660), the original phase 2 clinical trial results, even coupled with the recent additional *post hoc* analyses of the open-label extension study, and the similarly new and limited data on neuronal biomarkers (that pertain mostly to Alzheimer's disease), continue to present an exceedingly uncertain picture regarding AMX0035's effectiveness for the treatment of ALS.

[1] Food and Drug Administration. 22 Case Studies Where Phase 2 and Phase 3 Trials Had Divergent Results. January 2017. https://www.fda.gov/media/102332/download. Accessed September 19, 2022.

Despite a favorable advisory committee vote at the second meeting of the PCNS regarding AMX0035 on September 7, 2022, the FDA should not approve the drug because there is a lack of substantial evidence of effectiveness given the serious concerns and limitations identified by the agency's clinical and statistical reviewers regarding CENTAUR, its open-label extension study, and the related *post hoc* analyses presented by the sponsor. Instead, the agency should await the results of the ongoing phase 3 clinical trial of AMX0035 (PHOENIX) before considering approval of the drug. Approval of the drug based on the currently available data would further undermine the agency's standard for ensuring that new drugs are effective.

March 30, 2022, advisory committee meeting

On the question regarding whether CENTAUR and its open-label extension study established a conclusion that sodium phenylbutyrate/taurursodiol is effective in the treatment of patients with ALS, the PCNS members voted 4 Yes, 6 No at their March 30, 2022, meeting.[2] The majority of the PCNS members who voted in the negative agreed with FDA reviewers that the data from the CENTAUR trial and its open-label extension study were not sufficiently persuasive regarding the drug's effectiveness. The following is a list of several weaknesses regarding the CENTAUR trial's results:

(1) "[T]he statistical evidence (p=0.034) is not persuasive and there are additional questions about the robustness of the results."[3] This conclusion by FDA reviewers pertains to the primary outcome results showing an average 2.32-point treatment difference on the 48-point ALS functional scale after the conclusion of the six-month randomized trial.

(2) Reanalysis using a quadratic for time rendered the primary outcome nonsignificant (effect estimate=1.68 points on the ALS functional scale, p=0.1134).[4]

(3) Early unavailability of placebo prevented randomization of the first 18 subjects, and the subsequent nine subjects were then all assigned to placebo. Thus, the randomization process was compromised for the first 27 subjects (20% of the entire trial population) with a large proportion of the subjects being converted in the sponsor's reported analyses from "as-randomized" to "as-treated."[5]

(4) Post-baseline use of two other ALS medications (edaravone or riluzole) was markedly more frequent in the AMX0035 treatment group than the placebo group (15.7% vs. 4.2%), potentially biasing the results in favor of the former group.[6]

[2] Food and Drug Administration. Final summary minutes of the Peripheral and Central Nervous System Drugs Advisory Committee meeting. March 30, 2022. https://www.fda.gov/media/157745/download. Accessed September 22, 2022.
[3] Food and Drug Administration. Combined FDA and applicant briefing document for the meeting of the Peripheral and Central Nervous System Drugs Advisory Committee. March 30, 2022. https://www.fda.gov/media/157186/download. Accessed September 21, 2022. PDF p. 47.
[4] *Ibid.*
[5] *Id.* PDF p. 48.
[6] *Id.* PDF p. 47.

(5) The FDA specifically stated that the open-label extension study results were "difficult to interpret" because the protocol was unclear regarding the maintenance of subject and investigator blinding, and because a substantial proportion of the intention-to-treat subject population did not participate in the open-label study (37% of AMX0035-group subjects and 29% of placebo-group subjects).[7]

These issues and others led FDA reviewers to conclude that "The overall lack of statistical persuasiveness of the survival benefit, as well as the lack of replication of the results[,] raises concern that the modest survival benefit seen may potentially be due to underlying disease heterogeneity rather than an effect of the drug."[8]

September 7, 2022, PCNS meeting

Despite the negative review from the March 30, 2022, advisory committee meeting, the sponsor was afforded an unusual second review by the PCNS on September 7, 2022, so that committee members could consider additional data, which the sponsor hoped would provide "confirmatory evidence" in support of approval.[9]

The so called "confirmatory evidence" that the sponsor presented at the September 7, 2022, PCNS meeting notably represented additional *post hoc* analyses of CENTAUR and its open-label extension study and, thus, carry with it many of the same design, implementation, and interpretability concerns previously highlighted by FDA reviewers.

These new analyses can be logically divided into three parts, and FDA reviews of these new data included the following substantive critiques that argue strongly against approval:

(1) Regarding the first new analyses presented by the sponsor that purported to use subjects as their own controls, FDA reviewers noted the following problems:

(a) "[T]his 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."[10]

(b) "[I]t 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."[11]

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[7] *Id.* PDF pp. 65, 78.
[8] *Id.* PDF p. 78.
[9] Food and Drug Administration. Meeting of the Peripheral and Central Nervous System Drugs Advisory Committee. September 7, 2022. https://www.youtube.com/watch?v=6PMOyqd6WfA. Accessed September 21, 2022. See 43:10 to 43:46.
[10] Food and Drug Administration. FDA briefing document for the meeting of the Peripheral and Central Nervous System Drugs Advisory Committee (PCNS) Meeting. September 7, 2022. https://www.fda.gov/media/161378/download. Accessed September 21, 2022. PDF p. 10.
[11] *Ibid.*

(c) The analysis did not truly use subjects as their own controls, but instead continued to rely on less certain group analysis that compared multiple subjects on AMX0035 with multiple subjects on placebo. Accordingly, the results are more uncertain than true within-subject analyses.[12]

(d) "The pre-study slope was not directly measured and was calculated based on retrospectively collected data…

- The variability of the change in slope may not be constant…
- 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.
- 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.
- There is no way to check linearity of the pre-randomization slope."[13]

FDA reviewers thus concluded that "these data appear limited in their ability to provide independent substantiation for the observed effect on…the primary endpoint."[14]

(2) The second set of new analyses aim to consider the open-label survival results using two different methods, one with natural history comparison data and the other that estimated overall survival using a rank-preserving structural failure time model (RPSFTM).[15]

(a) Regarding the natural history survival analysis, FDA reviewers noted the following:

> "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 [intention-to-treat] 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 [open-label extension]." [16]

[12] *Ibid.*
[13] *Ibid.*
[14] *Ibid.*
[15] *Id*. PDF p. 11.
[16] *Id*. PDF p. 12

(b) Regarding the RPSFTM analysis, which provides an estimate of overall survival time for the placebo group, had treatment switching to AMX0035 not occurred,[17] FDA reviewers stated the following:

> "The presented RPSFTM analysis is not independent data and is simply using a new method of 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 [open-label extension]. 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 [open-label extension] 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 wider and the p-value is the same as from the ITT analysis based on the randomized groups…[18]
>
> "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 [open-label extension study]. 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).[19]
>
> "Furthermore, [many] best practices for the RPSFTM analysis were not implemented in this situation."[20]

Accordingly, FDA reviewers concluded that "FDA does not find these data [from the additional *post hoc* mortality analyses] sufficiently independent or persuasive to serve as independent confirmatory evidence of effectiveness."[21]

[17] *Ibid.*
[18] *Id.* PDF pp. 13-14.
[19] *Id.* PDF p. 14.
[20] *Ibid.*
[21] *Id*. PDF p. 15.

(3) Finally, the sponsor introduced new data regarding 18 biomarkers (cerebrospinal fluid assays) for a population engaged in a separate trial of AMX0035 as a treatment for Alzheimer's disease, not ALS.[22] FDA reviewers noted the following regarding these biomarker data:

(a) Those markers were only tested in Alzheimer's disease (AD) patients, so their relevance to ALS is unconfirmed.[23]

(b) The results were "…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 of nervous system inflammation or neuronal degeneration… It is unclear if these findings, even if they were demonstrated to be indicative of benefits in AD, would be generalizable to ALS."[24]

In summary, the three new *post hoc* analyses combined with the CENTAUR results fail to provide substantial evidence of effectiveness of AMX0035.

Introductory comments by senior FDA official unduly influenced, misdirected the majority of PCNS members

Despite the many serious limitations and problems outlined in detail by the FDA clinical and statistical reviewers regarding the data from CENTUAR, its open-label extension study, and the additional *post hoc* analyses offered by the sponsor, a 7-to-2 majority of members voted in favor of approval of AMX0035 for treatment of ALS at the September 7, 2022, PCNS meeting.

We are concerned that many committee members who voted in favor of approval chose to disregard the detailed FDA critiques of the AMX0035 clinical trial data because they were unduly swayed by comments made by the FDA's Billy Dunn, M.D., Director of the Office of Neuroscience, Office of New Drugs, Center for Drug Evaluation and Research, during his introductory presentation for this meeting. Particularly troubling was the following extraordinary query made by Dr. Dunn near the conclusion of his introductory presentation:

"[Amylyx Pharmaceuticals] has clearly indicated its awareness of the relevance of the PHOENIX study, stating publicly that it understands that continued approval in Canada is contingent upon success in PHOENIX. Arguably, that should make is easy for the company to make a similar public statement concerning the prospect of an approval of the current application. Given that a company can choose to voluntarily withdraw a product from marketing, it would seem the committee may be interested in a clear understanding of the sponsor's intent in seeking approval now while PHOENIX is ongoing, and I call on the company's co-CEOs [Justin Klee and Joshua Cohen] to state for the committee whether the

[22] *Ibid.*
[23] *Id*. PDF p. 16.
[24] *Ibid.*

> company would voluntarily withdraw [AMX0035] from marketing if the PHOENIX study does not succeed, should their current application ultimately be approved."[25]

Not surprisingly, Mr. Klee moments later stated the following:

> "Before we begin our formal presentation — this is Justin Klee, co-CEO and co-founder of Amylyx Pharmaceuticals and with me is Joshua Cohen co-CEO and co-founder of Amylyx Pharmaceuticals — Thank you Dr. Dunn for your remarks, and we would like to address them. To be clear, if PHOENIX is not successful, we will do what is right for patients, which includes voluntarily removing the product form the market."[26]

The unprecedented exchange between Dr. Dunn and Mr. Klee appears to have been scripted before the advisory committee meeting. Disturbingly, this exchange between Dr. Dunn and the sponsor's co-CEOs likely encouraged some committee members to gloss over the many serious limitations and problems with the AMX0035 study data described by FDA reviewers.

Importantly, the verbal assurance provided by Amylyx Pharmaceuticals's co-CEOs is not legally binding, nor should it be reassuring to consumers and patients. If Amylyx Pharmaceuticals were acquired by another company, that company could easily disregard such verbal assurances.

One member of the committee, G. Caleb Alexander, M.D., M.S., Johns Hopkins Bloomberg School of Public Health, added the following insightful comment regarding the withdrawal of approved drug products from the market:

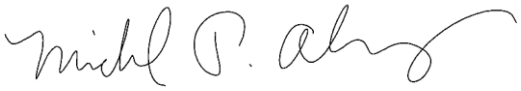
> "Although admittedly in rare cases manufacturers themselves have made the decision [to voluntarily withdraw a drug from the market], but regardless as we heard from the FDA, you know, whether or not they can ultimately pull a product from the market, it's no substitute for the evidentiary thresholds that are required for market access."[27]

The skewed framing by Dr. Dunn notwithstanding, the facts summarized and enumerated above do not support a conclusion that there is substantial evidence of effectiveness of AMX0035 for the treatment of ALS. Accordingly, we urge the FDA to not approve AMX0035 for ALS at this time.

[25] Food and Drug Administration. Meeting of the Peripheral and Central Nervous System Drugs Advisory Committee. September 7, 2022. https://www.youtube.com/watch?v=6PMOyqd6WfA. Accessed September 21, 2022. See 1:10:17 to 1:11:16.
[26] *Id.* See 1:16:41 to 1:17:10.
[27] *Id.* See 7:00:25 to 7:00:42.

Thank you for your attention to this important matter.

Sincerely,



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