Still a Lack of Substantial Evidence of Effectiveness for NDA# 216660, AMX0035 (Sodium Phenylbutyrate and Taurursodiol) for Treatment of Amyotrophic Lateral Sclerosis

Testimony Before the Food and Drug Administration's Peripheral and Central Nervous System (PCNS) Drugs Advisory Committee

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I am Michael Abrams from Public Citizen's Health Research Group. I have no conflicts of interest.

At present, we oppose Food and Drug Administration (FDA) approval of AMX0035 as a treatment for amyotrophic lateral sclerosis (ALS).

We agree with the critiques of FDA scientists detailed in their briefing document[1] for this second advisory committee meeting on this drug.

Specifically, in their first new analysis, the sponsor used subjects as their own controls to compare response rates in the active drug group to those in the placebo group.[2] The FDA noted several limitations:

(1) This *post hoc* analysis was not independent from the primary analysis of the CENTAUR trial and thus cannot be considered confirmatory evidence.[3]
(2) The basis for comparing the treatment effect at 18 months, instead of 24 months (the primary analysis endpoint), was unclear and inflated that effect.[4]
(3) The analysis did not truly use subjects as their own controls.[5]
(4) Slope calculation assumptions were suspect.[6]

The FDA concluded that "these data appear limited in their ability to provide independent substantiation for the observed effect on [the primary endpoint (*sic*).]"[7]

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[1] FDA Briefing Document NDA# 216660. Drug Name: AMX0035/sodium phenylbutyrate (PB) and taurursodial (TURSO). Applicant: Amylyx Pharmaceuticals. Peripheral and Central Nervous System Drugs Advisory Committee (PCNS) Meeting. September 7, 2022.https://www.fda.gov/media/161378/download. Accessed September 2, 2022.
[2] *Id*. PDF p. 8.
[3] *Id*. PDF p. 10.
[4] *Ibid*.
[5] *Ibid*.
[6] *Ibid*.
[7] *Ibid*.

The second set of new analyses aimed to confirm the survival results using two different methods, one with historical comparison data and the other that estimated survival using the rank-preserving structural failure time model (here after: rank-preserving).[8]

These analyses were deemed flawed by the FDA reviewers.

Specifically, the FDA noted the following regarding the natural history survival data analysis:

(1) This was not a randomized comparison.[9]
(2) Comparisons were made to controls from outside of the CENTAUR trial.[10]
(3) The analysis was not prespecified.[11]
(4) There are concerns about multiplicity.[12]

Regarding the rank-preserving analysis, the FDA noted that it was not based on "independent data and is simply using a new method of analyzing the same survival data presented in the original NDA submission."[13]

Moreover, specific limitations of this rank-preserving method include:

(1) Biased re-censoring in favor of the treatment group.[14]
(2) The unrealistic assumption that the treatment effect was proportional to time on drug, regardless of drug start time.[15]

Accordingly, the FDA stated it "does not find these data [from the additional post hoc mortality analyses] sufficiently independent or persuasive to serve as independent confirmatory evidence of effectiveness."[16]

The final data analysis introduced by the sponsor examined biomarkers pertaining to Alzheimer's disease. We agree with the FDA that the multiplicity of laboratory tests (n=18) is questionable regarding the treatment of Alzheimer's disease, and even more speculative (indeed untested) as markers for ALS treatment effectiveness.[17]

In conclusion, the new *post hoc* analyses of data from the already deficient CENTAUR trial fail to provided adequate confirmatory evidence of AMX0035's effectiveness as a treatment for ALS. Accordingly, we recommend that the committee vote "no" on the voting question before you today, and that the FDA not approve this medication for the treatment of ALS.

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[8] *Id*. PDF p. 11.
[9] *Id*. PDF p. 12.
[10] *Ibid*.
[11] *Ibid*.
[12] *Ibid*.
[13] *Id.* PDF p. 13.
[14] *Id.* PDF p. 14.
[15] *Id.* PDF p. 15.
[16] *Ibid*.
[17] *Id*. PDF p. 16.