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 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.

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We agree with the critique of FDA scientists detailed in the briefing document.

The phase 2 trial of interest enrolled only 137 subjects. Early problems with the placebo supply prevented randomization of the first 27 subjects.[1] Summary statistical values were marginal, primary-endpoint effect sizes modest, dropout rates high, and statistical modeling questionable.[2] The sponsor disregarded the FDA's recommendation to use the joint-rank analysis of function and survival for efficacy.[3] Analyses of secondary endpoints did not show any benefit.[4]

As with many small trials, group imbalances in baseline disease characteristics and post-enrollment initiation of other drugs plausibly compromised study validity and may have biased the primary efficacy results.[5]

The subsequent open-label extension study, according to FDA scientists, was "difficult to interpret" and "not persuasive" because of its open-label design, potential unblinding, substantial subject dropout rate, and flawed statistical analyses.[6]

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[1] Food and Drug Administration. Combined FDA and Applicant Briefing Document for NDA#21666, AMX0035/sodium phenylbutyrate (PB) and taurursodiol (TURSO), Amylyx Pharmaceuticals, Inc., Peripheral and Central Nervous System Drugs Advisory Committee (PCNS) Meeting. March 30, 2022. https://www.fda.gov/media/157186/download. Accessed March 30, 2022. PDF p. 48.
[2] *Ibid.* PDF pp. 30, 47, 49, 50, and 96.
[3] *Ibid.* PDF pp. 16, 24, 27, 48.
[4] *Ibid.* PDF p. 97.
[5] *Ibid.* PDF pp. 40-1 and 43.
[6] *Ibid.* PDF pp. 12, 65, 78, and 82.

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Per the FDA's penultimate briefing statement, the agency may rely on "a single, large, multicenter trial to establish effectiveness." However, the FDA also appropriately stated that such reliance "should generally be limited to trials that demonstrated a clinically meaningful and statistically very persuasive effect on mortality,"[7] which was not the case for AMX0035.

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Notably, in 2017, the FDA published a report documenting numerous cases of favorable phase 2 clinical trial results not being confirmed in subsequent phase 3 trials.[8] Such a scenario is highly likely for AMX0035.

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In conclusion, there is a lack of substantial evidence of effectiveness for AMX0035 for treating ALS. The FDA must wait for the results of the ongoing phase 3 trial before considering approval of this drug.

We thus urge the advisory committee members to vote "No" on the key question before you today.

Finally, although the FDA "has long stressed the appropriateness of exercising regulatory flexibility in applying the statutory standards to drugs for serious disease with unmet medical need," it must do so "while preserving appropriate assurance of safety and effectiveness."[9] In this case, such flexibility is unacceptable given the lack of assurance of effectiveness.

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[7] *Ibid.* PDF p. 97.

[8] U.S. Food & 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 March 30, 2022.

[9] Food and Drug Administration. Combined FDA and Applicant Briefing Document for NDA#21666, AMX0035/sodium phenylbutyrate (PB) and taurursodiol (TURSO), Amylyx Pharmaceuticals, Inc., Peripheral and Central Nervous System Drugs Advisory Committee (PCNS) Meeting. March 30, 2022. https://www.fda.gov/media/157186/download. Accessed March 30, 2022. PDF p. 12.