October 24, 2022

Michael T. Abrams, M.P.H., Ph.D.
Senior Health Researcher
Public Citizen's Health Research Group

Michael A. Carome, M.D.
Director
Public Citizen's Health Research Group

Dear Drs. Abrams and Carome:

Thank you for your letter, dated September 23, 2022, to Dr. Califf, Commissioner, Food and Drug Administration, in which you urged the FDA not to approve AMX0035 (sodium phenylbutyrate and taurursodiol) to treat amyotrophic lateral sclerosis (ALS) because the available data fail to provide substantial evidence of effectiveness.

As you are likely aware, on September 29, 2022, the FDA's Office of Neuroscience in the Center for Drug Evaluation and Research approved Relyvio to treat patients with ALS. The decision to approve the drug was based on the review of the application, including the AMX3500 study, demonstrating a statistically significant treatment of benefit compared to the placebo on the pre-specified primary endpoint, the rate of decline of ALSFRS-R, indicating a slowing of disease progression. Confirmatory evidence to support this single trial included a post hoc exploratory analyses observing an overall survival benefit. For additional information on the basis for approval, including our final assessment of the issues that you raised, I refer you to the summary memo supporting our approval available on our website.

You also express concern that the Advisory Committee members were unduly swayed by comments made by FDA's Billy Dunn, M.D. during his introductory presentation for the meeting. You were particularly troubled by the question posed by Dr. Dunn to the sponsor regarding whether they would withdraw the drug should the follow up PHOENIX study be negative and state that the exchange "appears to have been scripted." To clarify the record, it was not scripted. Further, while you focus on a part of Dr. Dunn's opening statement, you fail to note the important points made by Dr. Dunn about FDA's regulatory responsibility to exercise appropriate flexibility to expedite the development, evaluation, and marketing of new therapies intended to treat persons with life-threatening and severely debilitating diseases, especially where no satisfactory alternative therapy exists (21 C.F.R. Subpart E). Consistent with this regulatory framework, FDA determined that although data supporting the application results in a degree of residual uncertainty about the evidence of effectiveness that exceeds that which might typically remain following a conclusion that substantial evidence of effectiveness has been demonstrated; given the serious and life-threatening nature of ALS and the substantial unmet need, this level of uncertainty is acceptable in this instance (see summary memo). Dr. Dunn's statement was consistent with statements in FDA's draft guidance on Demonstrating Substantial Evidence of Effectiveness, regarding when less certainty about

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effectiveness may be acceptable, when balanced against the risk of rejecting or delaying the marketing of an effective therapy.

Finally, members of our Advisory Committee are chosen because of their expertise and leadership in their field, and we value their independent judgement. The Committee was presented with a balanced assessment of the data and regulatory framework within which we operate, and we have confidence that they drew their conclusions based on their independent assessment of all considerations.

Sincerely,

Patrizia A. Cavazzoni -S

Digitally signed by Patrizia A. Cavazzoni -S
Date: 2022.10.24 13:16:15 -04'00'

Patrizia Cavazzoni, M.D.
Director, Center for Drug Evaluation and Research

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