Food and Drug Administration
Center for Drug Evaluation and Research
Final Summary Minutes of the Peripheral and Central Nervous System Drugs Advisory Committee Meeting
September 7, 2022

Location: Please note that due to the impact of this COVID-19 pandemic, all meeting participants joined this advisory committee meeting via an online teleconferencing platform.

Topic: The committee discussed new drug application (NDA) 216660, for sodium phenylbutyrate/taurursodiol (AMX0035) powder for oral suspension, submitted by Amylyx Pharmaceuticals Inc., for the treatment of amyotrophic lateral sclerosis.

These summary minutes for the September 7, 2022 meeting of the Peripheral and Central Nervous System Drugs Advisory Committee of the Food and Drug Administration were approved on 9/30/2022.

I certify that I attended the September 7, 2022 meeting of the Peripheral and Central Nervous System Drugs Advisory Committee (PCNS) of the Food and Drug Administration and that these minutes accurately reflect what transpired.

/s/	**/s/**
Jessica Seo, PharmD, MPH	Thomas J. Montine, MD, PhD
Designated Federal Officer, PCNS	Chairperson, PCNS

Final Summary Minutes of the Peripheral and Central Nervous System Drugs Advisory Committee Meeting
September 7, 2022

The Peripheral and Central Nervous System Drugs Advisory Committee (PCNS) of the Food and Drug Administration, Center for Drug Evaluation and Research, met on September 7, 2022. The meeting presentations were heard, viewed, captioned, and recorded through an online teleconferencing platform. Prior to the meeting, the members and temporary voting members were provided the briefing materials from the FDA and Amylyx Pharmaceuticals, Inc. The meeting was called to order by Thomas J. Montine, MD, PhD (Chairperson). The conflict of interest statement was read into the record by Jessica Seo, PharmD, MPH (Designated Federal Officer). There were approximately 1520 people online. There were a total of twenty-three Open Public Hearing (OPH) speaker presentations.

A verbatim transcript will be available, in most instances, at approximately ten to twelve weeks following the meeting date.

Agenda:

The committee discussed new drug application (NDA) 216660, for sodium phenylbutyrate/taurursodiol (AMX0035) powder for oral suspension, submitted by Amylyx Pharmaceuticals Inc., for the treatment of amyotrophic lateral sclerosis.

Attendance:

Peripheral and Central Nervous System Drugs Advisory Committee Members Present (Voting): Thomas J. Montine, MD, PhD (*Chairperson*); G. Caleb Alexander, MD, MS; Robert C. Alexander, MD; Liana G. Apostolova, MD, MSc, FAAN

Peripheral and Central Nervous System Drugs Advisory Committee Members Not Present (Voting): Merit E. Cudkowicz, MD; Dawndra Jones, RN, DNP (*Consumer Representative*); Richard J. Kryscio, PhD; Michelle M. Mielke, PhD

Peripheral and Central Nervous System Drugs Advisory Committee Member Not Present (Non-Voting): Michael Gold, MS, MD (*Industry Representative*)

Temporary Members (Voting): Kenneth Fischbeck, MD; Dean Follmann, PhD; Avindra Nath, MD; Bryan J. Traynor, MD, PhD; Mark Weston (*Patient Representative*)

Acting Industry Representative to the Committee (Non-Voting): Jeffrey M. Dayno, MD (*Acting Industry Representative*)

FDA Participants (Non-Voting): Billy Dunn, MD; Teresa Buracchio, MD; Emily Freilich, MD;

Designated Federal Officer (Non-Voting): Jessica Seo, PharmD, MPH

Open Public Hearing Speakers Present: Zachary Simmons, MD; Terry Heiman-Patterson, MD; William (Bill) Woods, MD; Samuel Maiser, MD (Hennepin Healthcare and the Twin Cities ALS Research Consortium); Daragh Heitzman, MD, FAAN; Kelly G. Gwathmey, MD; James Wymer; Vance Burghard; Gary L. Pattee, MD; Greg Canter; Gwen Petersen; Shafeeq S. Ladha, MD; Steve Kowalski; Scott Kauffman (ALS Association); Christa Thompson; Andrea Pauls Backman, MBA (Les Turner ALS Foundation); Jinsy Andrews, MD, MSc; Paul Melmeyer (Muscular Dystrophy Association); Richard Bedlack, MD, PhD; Michael Abrams, MPH, PhD (Public Citizen); Brian Wallach and Evie Kling; Jeff Derby; Diana Zuckerman (National Center for Health Research)

The agenda was as follows:

Call to Order and Introduction of Committee	***Thomas J. Montine, MD*** *Chairperson, PCNS*
Introduction of Committee and Conflict of Interest Statement	***Jessica Seo, PharmD, MPH*** *Designated Federal Officer, PCNS*
FDA Introductory Remarks	***Billy Dunn, MD*** *Director, Office of Neuroscience (ON)* *Office of New Drugs (OND), CDER, FDA*
APPLICANT PRESENTATIONS	***Amylyx Pharmaceuticals, Inc.***
Introduction	***Tammy Sarnelli, MPAHC*** *Global Head, Regulatory Affairs* *Amylyx Pharmaceuticals*
Current Landscape in ALS	***Sabrina Paganoni, MD, PhD*** *Co-Director, Neurological Clinical Research Institute* *Sean M. Healey and AMG Center for ALS* *Massachusetts General Hospital* *Associate Professor, Harvard Medical School*
Biomarker Data	***Lahar Mehta, MD*** *Head of Global Clinical Development* *Amylyx Pharmaceuticals*
CENTAUR Results and New Overall Survival Analyses	***Jamie Timmons, MD*** *Head of Scientific Communications* *Amylyx Pharmaceutical*

Clinical Perspective

Merit E. Cudkowicz, MD, MSc
Chief, Neurology Department and Director
Sean M. Healey and AMG Center for ALS
Massachusetts General Hospital
Julieanne Dorn Professor of Neurology
Harvard Medical School

Clarifying Questions to the Applicant

BREAK

FDA PRESENTATIONS

FDA Overview

Teresa Buracchio, MD
Director
Division of Neurology 1 (DN 1)
ON, OND, CDER, FDA

Tristan Massie, PhD
Biostatistics Reviewer
Division of Biostatistics 1
Office of Biostatistics
Office of Translational Sciences, CDER, FDA

Emily Freilich, MD
Cross Discipline Team Leader
DN1, ON, OND, CDER, FDA

Clarifying Questions to FDA

OPEN PUBLIC HEARING

BREAK

Questions to the Committee/
Committee Discussion

ADJOURNMENT

Questions to the Committee:

1. **DISCUSSION:** Discuss the strength of the currently available data regarding the effectiveness of sodium phenylbutyrate/taurursodiol (AMX0035), to include the new information submitted and the information presented at the March 30, 2022, PCNS meeting.

The discussion may include considerations regarding the unmet need in amyotrophic lateral sclerosis (ALS), the status of the ongoing Phase 3 trial, and the seriousness of ALS.

***Committee Discussion**: The Committee members expressed a range of viewpoints when discussing the strength of the currently available data (including the new information submitted and the information presented at the March 30, 2022, PCNS meeting) regarding the effectiveness of sodium phenylbutyrate/taurursodiol (AMX0035). Some members were in agreement that the overall evidence presented from both meetings was mild to moderately persuasive of the effectiveness of AMX0035, noting that while the data presented has its limitations and challenges, the endpoints trend in the same direction and may support the finding of prolonged survival with the product. Other members expressed being reassured by the absence of a safety signal, suggesting that AMX0035 is not likely to harm patients even if the Phase 3 PHOENIX trial fails to demonstrate a benefit.*

Other members found the overall evidence less compelling. Several members were in agreement that the biomarker analysis did not add much to support evidence of effectiveness, with members pointing to shortcomings such as measurements being taken from one time point, and the unclear relevance of biomarker data derived from patients with Alzheimer's Disease to ALS. The committee members were divided when discussing the strength of the new sensitivity analyses using external natural history data presented by the Applicant. Some members were less compelled, pointing to the analyses being conducted post-hoc and not pre-specified, and questioning the source and population base used. Other members noted the analyses were supportive of a real-world difference in patients treated with AMX0035 and the observed survival benefit seemed to make sense, but acknowledged the limitations.

During the Committee's discussions, several members recognized the unmet medical need for treatment options for a rare and life-threatening condition such as ALS, with one member pointing to the importance of listening to the patient community and highlighting FDA's ability to exercise regulatory flexibility in this context. A few members discussed the financial aspect of market approval for AMX0035, and FDA clarified that the drug cost would not be a relevant consideration in the FDA's scientific deliberations and assessment of the scientific evidence.

Please see the transcript for details of the Committee's discussion.

2. **VOTE**: Considering the new information submitted and the information presented at the March 30, 2022, PCNS meeting, is the available evidence of effectiveness sufficient to support approval of sodium phenylbutyrate/taurursodiol (AMX0035) for the treatment of patients with ALS? In addition to the prior and new evidence presented, you may take into account in your vote the unmet need in ALS, the status of the ongoing Phase 3 trial, and the seriousness of ALS

   Vote Result: Yes: 7 No: 2 Abstain: 0

Committee Discussion: *The majority of the Committee members voted "Yes", indicating that the available evidence of effectiveness is sufficient to support approval of sodium phenylbutyrate/taurursodiol (AMX0035) for the treatment of patients with ALS. Several members who voted "Yes" acknowledged the seriousness of the disease, the unmet medical need for treatment options in a life-ending illness such as ALS, and the moving testimony of family members, patients with ALS, and the experts treating them, in contributing to their vote. The members who voted "No" were in agreement that the new information presented, combined with the evidence presented at the March 30, 2022 PCNS meeting, does not constitute substantial evidence of effectiveness to support approval of AMX0035 at this point. While also acknowledging the unmet medical need and seriousness of ALS, both of these members cited the use of a single study with scientific concerns (CENTAUR trial), and use of post-hoc analyses for confirmatory evidence that were not pre-specified, as reasons the threshold for substantial evidence of effectiveness has not been met for approval. Please see the transcript for details of the Committee's discussion.*

The meeting was adjourned at approximately 6:42 p.m. ET.