Food and Drug Administration
Center for Drug Evaluation and Research

Final Summary Minutes of the Peripheral and Central Nervous System Drugs Advisory Committee Meeting

March 30, 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 (ALS).

These summary minutes for the March 30, 2022 meeting of the Peripheral and Central Nervous System Drugs Advisory Committee of the Food and Drug Administration were approved on April 15, 2022.

I certify that I attended the March 30, 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 Designated Federal Officer, PCNS	Thomas J. Montine, MD, PhD Chairperson, PCNS

Final Summary Minutes of the Peripheral and Central Nervous System Drugs Advisory Committee Meeting
March 30, 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 March 30, 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 briefing materials and pre-recorded presentations 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 1,479 people online. There were a total of twenty-six 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 (ALS).

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; Dawndra Jones, RN, DNP (*Consumer Representative*)

Peripheral and Central Nervous System Drugs Advisory Committee Members Not Present (Voting): Merit E. Cudkowicz, MD; Richard J. Kryscio, PhD; Michelle M. Mielke, PhD; Bruce Ovbiagele, MD, MSc, MAS, MBA

Peripheral and Central Nervous System Drugs Advisory Committee Member (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*)

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: Jeff Derby; Vance Burghard; Michael Abrams, MPH, PhD (Public Citizen); Calaneet Balas (The ALS Association); Steve Kowalski; Richard Bedlack, MD, PhD; Diana Zuckerman, PhD (National Center for Health Research); Becky Mourey and Alexander Mourey; Javad Golji; Greg Canter; Andrea Pauls Backman (Les Turner ALS Foundation); Christa Thompson; Gwen Petersen; Katrina Byrd; Paul Melmeyer (Muscular Dystrophy Association); James Berry, MD; Phil Green and Sandy Morris; Juan A. Reyes; Laura Dalle Pazze (I AM ALS); Larry Falivena; John Russo and Loretta Russo; Scott L. Kauffman; Brian Wallach and Sandra Abreyava; Joel Shamaskin, MD; William G. Woods, MD; Mike Henson (No More Excuses ALS Watchdogs)

The agenda was as follows:

Call to Order	**Thomas J. Montine, MD, PhD** Chairperson, PCNS
Introduction of Committee and Conflict of Interest Statement	**Jessica Seo, PharmD, MPH** Designated Federal Officer, PCNS
FDA Introductory Remarks	**Teresa Buracchio, MD** Director Division of Neurology 1 (DN1) Office of Neuroscience (ON) Office of New Drugs (OND), CDER, FDA
APPLICANT PRESENTATIONS	**Amylyx Pharmaceuticals, Inc.**
Introduction	**Justin Klee and Joshua Cohen** Co-CEOs and Co-Founders Amylyx Pharmaceuticals
Clinical Trials in ALS	**Jeremy Shefner, MD, PhD** Kemper and Ethel Marley Professor and Chair of Neurology Barrow Neurological Institute
Benefit / Risk	**Jamie Timmons, MD** Head of Scientific Communications Amylyx Pharmaceutical
Clinical Perspective	**Sabrina Paganoni, MD, PhD** Co-Director, Neurological Clinical Research Institute and Healey & AMG Center for ALS, Massachusetts General Hospital Associate Professor, Harvard Medical School
Clarifying Questions to the Applicant	
BREAK	

FDA PRESENTATIONS

FDA Summary Presentations	**Emily Freilich, MD** Cross Discipline Team Leader DN1, ON, OND, CDER, FDA **Tristan Massie, PhD** Biostatistics Reviewer Division of Biostatistics 1 Office of Biostatistics Office of Translational Sciences, CDER, FDA
Clarifying Questions to FDA	

LUNCH

OPEN PUBLIC HEARING

BREAK

Questions to the Committee/Committee Discussion

ADJOURNMENT

Question to the Committee:

1. **VOTE**: Do the data from the single randomized, controlled trial and the open-label extension study establish a conclusion that sodium phenylbutyrate/taurursodiol is effective in the treatment of patients with amyotrophic lateral sclerosis (ALS)?

    a. If you voted "no", please discuss what additional information you would consider necessary to establish a conclusion that sodium phenylbutyrate/taurursodiol is effective in the treatment of patients with ALS

Vote Result: Yes: 4 No: 6 Abstain: 0

Committee Discussion: *A narrow majority of members voted "No," that the data from the single randomized, controlled trial and the open-label extension study did not establish a conclusion that sodium phenylbutyrate/taurursodiol is effective in the treatment of ALS. Those who voted "No" were in agreement that the data from the CENTAUR study did not meet the statutory and regulatory threshold for substantial evidence and persuasiveness, citing limitations such as small sample size, baseline imbalances, problems with randomization and blinding, and treatment of missing data. Several members also noted the modest effect on the primary endpoint and lack of statistical significance on the secondary endpoints. In addition, some members noted concerns with the open-label extension study, citing issues such as the absence of a control group, high rates of non-participation and drop-outs, and treatment of tracheostomies and hospitalizations as death equivalents and composite outcomes, all of which limit the study's ability to provide supportive evidence of effectiveness. Several members agreed that results from the ongoing*

Phase 3 PHOENIX trial would be needed to resolve many uncertainties surrounding the conclusions from the CENTAUR and open-label extension study.

Some members who voted "Yes" acknowledged that it was a difficult decision due to the concerns raised by the FDA, with one member ultimately agreeing with the appropriateness of the Applicant's primary analysis using the shared baseline linear random effects model. Other members were compelled by the unmet need for ALS treatment options, with one member suggesting the data shows AMX0035 appears to cause no material harm and persons living with ALS should be able to decide for themselves whether to accept the risk of taking a drug with uncertain benefit.

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

The meeting was adjourned at approximately 5:03 p.m. ET.