FOOD AND DRUG ADMINISTRATION

CENTER FOR DRUG EVALUATION AND RESEARCH

PERIPHERAL AND CENTRAL NERVOUS SYSTEM DRUGS ADVISORY COMMITTEE MEETING (PCNS)

Virtual Meeting

Wednesday, March 30, 2022

10:00 a.m. to 5:03 p.m.

Meeting Roster

DESIGNATED FEDERAL OFFICER (Non-Voting)

Jessica Seo, PharmD, MPH

Division of Advisory Committee and

Consultant Management

Office of Executive Programs, CDER, FDA

PERIPHERAL AND CENTRAL NERVOUS SYSTEM DRUGS

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C O N T E N T S

C O N T E N T S (continued)

P R O C E E D I N G S

(10:00 a.m.)

Call to Order

DR. MONTINE: Good morning and welcome. I wish to first remind everyone to please mute your line when you're not speaking. For media and press, the FDA press contact is April Grant. Her email and phone number are currently displayed.

My name is Tom Montine. I'm a professor at Stanford University, and I'll be chairing this meeting. I now call to order the March 30, 2020 Peripheral and Central Nervous System Drugs Advisory Committee. Dr. Jessica Seo is the designated federal official for this meeting and will begin with the introductions.

Introduction of Committee

DR. SEO: Good morning. My name is Jessica Seo, and I am the designated federal officer for this meeting. All voting members have confirmed via email that they have viewed the prerecorded presentation for today's meeting in their entirety. When I call your name, please introduce yourself by

stating your name and affiliation, and "I confirm."

We'll begin with Dr. Caleb Alexander.

DR. R. ALEXANDER: Good morning. This is Robert Alexander from the Banner Alzheimer's Institute in Phoenix, and I confirm. Thank you.

DR. SEO: Thank you, Dr. Robert Alexander.

I'll go back to Dr. Caleb Alexander. Please state your name and affiliation, please.

(No response.)

DR. SEO: Dr. Alexander, you may be muted.

DR. C. ALEXANDER: Good morning. This is Caleb Alexander. I'm a practicing general internist and professor of epidemiology and medicine at the Johns Hopkins Bloomberg School of Public Health.

DR. SEO: Thank you, sir.

Next we have Dr. Apostolova.

DR. APOSTOLOVA: Hello. This is Liana Apostolova. I'm a professor in neurology at the Indiana School of Medicine, the Indiana University School of Medicine, and I confirm.

DR. SEO: Thank you.

Dr. Gould?

DR. GOULD: Good morning. This is Dr. Michael Gould. I'm the non-voting industry representative, and I confirm.

DR. SEO: Thank you, sir.

Dr. Jones?

DR. JONES: Good morning. I am Dawndra Jones, and I'm the chief officer and vice president of patient services at [inaudible – audio gap].

DR. SEO: Thank you.

Dr. Montine?

DR. MONTINE: Good morning. My name is Tom Montine. I'm a professor at Stanford University, and I confirm.

DR. SEO: Thank you.

Dr. Fischbeck?

DR. FISCHBECK: Hi. This is Kenneth Fischbeck. I'm a neurologist in the National Institute of Neurological Disorders and Stroke at the NIH in Bethesda, and I confirm.

DR. SEO: Thank you.

Dr. Follmann?

DR. FOLLMANN: Yes. Good morning. My name is Dean Follmann. I'm head of biostatistics at the National Institute of Allergy and Infectious Diseases, and I confirm.

DR. SEO: Thank you.

Dr. Nath?

DR. NATH: Hi. This is Avi Nath. I'm the clinical director of the National Institute of Neurological Disorders and Stroke at NIH, and I confirm.

DR. SEO: Thank you.

Dr. Traynor?

DR. TRAYNOR: Hi. My name is Bryan Traynor. I'm a senior investigator at the National Institute on Aging at NIH, and I confirm.

DR. SEO: Thank you.

Next, Dr. Weston?

MR. WESTON: Good morning. My name is Mark Weston. I am the patient representative and a voting member of today's advisory committee meeting.

Briefly, my qualifications are that I was

diagnosed with sporadic limb onset ALS in October of 2019. Diagnosis was confirmed in December of 2019. My symptoms, however, given the benefit of 20/20 hindsight, may have begun as long ago as late 2017, more than 4 years ago, and I confirm.

DR. SEO: Thank you, sir.

We now have the FDA participants. I will begin with Dr. Dunn. Please introduce yourself.

DR. DUNN: Yes. My name is Billy Dunn. I'm the director of the Office of Neuroscience at FDA.

DR. SEO: Thank you.

Dr. Buracchio?

DR. BURACCHIO: Hi. I'm Teresa Buracchio. I'm director of the Division of Neurology 1 at FDA.

DR. SEO: And Dr. Freilich?

DR. FREILICH: Hi. This is Emily Freilich. I'm the cross-disciplinary team lead in the Division of Neurology 1 at FDA. Thank you.

DR. SEO: I'll hand it back to you, Dr. Montine.

DR. MONTINE: Thank you, Jessica.

For topics such as those being discussed at

today's meeting, there are often a variety of opinions, some of which are held quite strongly. Our goal today is that our meeting will be a fair and open discussion for these issues and that individuals can express their views without interruption. Thus, as a gentle reminder, individuals will be allowed to speak into the record only if recognized by the chair. We look forward to a productive meeting together.

In the spirit of the Federal Advisory Committee Act and the Government in the Sunshine Act, we ask that the advisory committee members take care that their conversations about the topic at hand take place in the open forum of the meeting.

We are aware that members of the media are anxious to speak with the FDA about these proceedings, however, FDA will refrain from discussing the details of this meeting with the media until its conclusion. Also, the committee is reminded to please refrain from discussing the meeting topic during breaks or lunch. Thank you.

Now, Dr. Jessica Seo will read the Conflict of Interest Statement for the committee.

Conflict of Interest Statement

DR. SEO: Thank you, Dr. Montine.

The Food and Drug Administration, or FDA, is convening today's meeting of the Peripheral and Central Nervous System Drugs Advisory Committee under the authority of the Federal Advisory Committee Act of 1972. With the exception of the industry representative, all members and temporary voting members of the committee are special government employees, or SGEs, or regular federal employees from other agencies and are subject to federal conflict of interest laws and regulations.

The following information on the status of this committee's compliance with federal ethics and conflict of interest laws, covered by but not limited to those found at 18 U.S. Code Section 208, is being provided to participants in today's meeting and to the public.

FDA has determined that members and temporary voting members of this committee are in

compliance with federal ethics and conflict of interest laws. Under 18 U.S. Code Section 208, Congress has authorized FDA to grant waivers to special government employees and regular federal employees who have potential financial conflicts when it is determined that the agency's need for a special government employee's services outweighs his or her potential financial conflict of interest or when the interest of a regular federal employee is not so substantial as to be deemed likely to affect the integrity of the services which the government may expect from the employee.

Related to the discussions of today's meeting, members and temporary voting members of this committee have been screened for potential financial conflicts of interests of their own as well as those imputed to them, including those of their spouses or minor children and, for purposes of 18 U.S. Code Section 208, their employers. These interests may include investments; consulting; expert witness testimony; contracts, grants, CRADAs; teaching, speaking, writing;

patents and royalties; and primary employment.

Today's agenda involves a discussion of new drug application 216660 for sodium phenylbutyrate and taurursodiol, known as AMX0035, powder for oral suspension, submitted by Amylyx Pharmaceuticals, Incorporated, for the treatment of amyotrophic lateral sclerosis or ALS.

This is a particular matters meeting during which specific matters related to Amylyx Pharmaceuticals' NDA will be discussed. Based on the agenda for today's meeting and all financial interests reported by the committee members and temporary voting members, no conflicts of interest have been issued in connection with this meeting. To ensure transparency, we encourage all standing committee members and temporary voting members to disclose any public statements that they have made concerning the product at issue.

With respect to FDA's invited industry representative, we would like to disclose that Dr. Michael Gould is participating in this meeting as a non-voting industry representative acting on

behalf of regulated industry. Dr. Gould's role at this meeting is to represent industry in general and not any particular company. Dr. Gould is employed by AbbVie.

We would like to remind members and temporary voting members that if the discussions involve any other product or firms not already on the agenda for which an FDA participant has a personal or imputed financial interest, the participants need to exclude themselves from such involvement, and their exclusion will be noted for the record. FDA encourages all other participants to advise the committee of any financial relationships that they may have with the firm at issue. Thank you.

DR. MONTINE: Thank you, Jessica.

We will now proceed with the FDA introductory remarks from Dr. Teresa Buracchio.

FDA Introductory Remarks – Teresa Buracchio

DR. BURACCHIO: Thank you, Dr. Montine.

Welcome to our committee members and guests who are joining us for this important meeting. I

would like to thank the committee for the time that they have taken from their busy work schedule to review the advance materials and for joining us today to discuss the important topics that are under consideration for this application. We greatly value your perspectives and input.

I would also like to thank the public attendees, and especially the ALS patients who are joining us today. Your attendance and commitment to finding a treatment for ALS are immensely appreciated. For those of you who will address the committee later today, or have provided written comments for the committee, we look forward to and are deeply appreciative of your input.

We are here today to discuss the development of AMX0035, also referred to as sodium phenylbutyrate, taurursodiol, for the treatment of patients with ALS. We at FDA appreciate our interactions with the ALS patient community. We have been very engaged with the ALS patient community, along with scientific and advocacy leaders in this area, and we have benefited

enormously from the perspectives that have been shared with us.

We recognize that ALS is a devastating disease that takes a punishing toll on the patients and their loved ones. Although there are approved therapies, we also recognize that there is an urgent unmet need for therapies that slow or stop this relentless disease. We have also heard from many patients that they consider even small treatment benefits to be meaningful in this terrible disease, and that their tolerance for risk is high.

I want to assure both the ALS community and the committee that we at the FDA have heard the concerns of the ALS community and are responsive to them. I also want to assure the committee that although the applicant and FDA have different views on the data that will be discussed today, we have always considered the context of the unmet need in ALS with this application and in the regulatory interactions that have preceded this submission.

In the neurology divisions, a substantial

portion of the development programs that we oversee are for severely debilitating and progressive neurodegenerative diseases that have similar concerns, so these issues are not unfamiliar to us and we are mindful of them. We make a point to consider this context in all our interactions with sponsors throughout the development process.

I would like to explicitly note that our concerns with this application described in the briefing package and recorded presentation, and that will be further discussed today, exist even with the recognition that ALS is a rare disease with a relentlessly progressive course that has an enormous unmet medical need. Even in the face of these needs, we have concerns about the analyses and the interpretation of the data from a single small clinical trial, and whether these data provide substantial evidence of effectiveness of AMX0035.

Before describing some of the issues we will ask you to discuss today, I want to stress that we have not made any final decisions on the

approvability of this application. Our comments in the background package are preliminary and do not yet take into account today's proceeding. Our concern should not be viewed as necessarily indicative of our final decision. The reason we are here today is to gain your input into some of the challenging issues we have faced during our review process so that we may incorporate it into our decision on approvability.

I will now provide some background on the development program for AMX0035 and the issues for discussion that bring us here today. AMX0035 is a fixed combination of sodium phenylbutyrate and taurursodiol. The applicant theorizes that AMX0035 reduces endoplasmic reticulum stress and improves mitochondrial function and energy production.

The division notes that dysfunction of the endoplasmic reticulum and mitochondria are some of many potential processes hypothesized to be involved in the pathophysiology of ALS, however, the pathophysiology of ALS remains unknown.

The applicant conducted a single 24-week,

double-blind, placebo-controlled phase 2 study, AMX3500, which the sponsor also called CENTAUR, in 137 patients with ALS. The applicant reported a positive result on the primary endpoint, a commonly used functional endpoint in ALS, the ALS Functional Rating Scale-Revised, which is abbreviated as the ALSFRS-R.

The use of the ALSFRS-R scale as a primary endpoint is common, but you will hear that we have significant concerns with the appropriateness of the prespecified analysis method. We will also discuss other important factors with the conduct of the design of the study that could have influenced study outcomes and raise concerns regarding the robustness of the study results. It is also important to note that there was no survival benefit reported in the initial 24-week CENTAUR study.

After the completion of the study, the applicant asked to meet with the division because the applicant felt that the study results would be capable of supporting a new drug application.

After careful detailed review of the sponsor's data, the division noted that the prespecified statistical result was not exceptionally persuasive and that there were issues with the analysis and robustness of the data.

The division noted that the data presented by the sponsor, though promising, did not appear adequate to serve as a single study capable of providing substantial evidence of effectiveness and recommended that a second study would be needed to confirm the study results.

The applicant continued to evaluate data from the open-label extension study of CENTAUR. The applicant conducted survival analysis based on data cutoffs of February 2020 and July 2020. These dates were not prespecified in the initial statistical analysis plan for the open-label extension.

So the survival analysis plan and subsequent amendment were finalized in March 2020 and August 2020, respectively. It should be noted that these statistical analysis plans for survival were

finalized after the data cutoff dates that were proposed in the analysis plan and after the results of the randomized phase of the CENTAUR study were known. It's also notable that the results of the February 2020 analysis were known at the time of the July 2020 analysis.

The February 2020 analysis was conducted to support a meeting request to FDA and showed a non-significant trend for a survival benefit in patients who had received AMX0035 in the randomized trial compared to patients who had received placebo in the trial.

The results of the July 2020 analysis were reported to show the nominally significant apparent survival benefit in patients who received AMX0035 in the randomized trial compared to those who received placebo. The results in the July 2020 cutoff date were subsequently reported and published.

The applicant met with the division once again to discuss whether the study results from the CENTAUR study and the open-label extension could be

capable of supporting a new drug application. The division noted multiple concerns with the interpretability of the reported survival benefit that was assessed using a variety of composite endpoints and death alone.

These concerns included the small sample size; the large number of dropouts in the open-label extension period; the inclusion of tracheostomies in hospitalizations that are not equivalent to death in the composite survival outcomes; and the multiple survival analyses which had previously been reported as negative.

A spurious finding on the survival analysis could not be ruled out. The division again recommended that a second study would be needed to confirm these results. It is critical to note that the applicant has recently initiated a phase 3 study in 600 patients worldwide. It is currently enrolling and is expected to complete in late 2023. The division continues to feel that this study is crucial for the assessment of the efficacy of AMX0035 in ALS.

Although the concerns with the data and analyses from the randomized trial and open-label extension remain, the division continued to consider the reported survival benefit on the endpoint of death alone and felt that the data should be assessed in the context of an application review, including discussion with this committee. The division subsequently invited the applicant to submit an NDA prior to completion of the ongoing phase 3 study to allow for this review and discussion.

I would like to note that we have no substantial concerns with the safety of AMX0035, and so our discussion today will focus on whether the efficacy data are adequate to conclude that AMX0035 is effective for the treatment of ALS. To inform this discussion, I would now like to briefly describe the approval standards for establishing the effectiveness of a drug.

As required by law, FDA must determine that there is substantial evidence of effectiveness for AMX0035 for approval. The term "substantial

evidence" was carefully defined in Section 505(b) of the Food, Drug, and Cosmetic Act as evidence consisting of adequate and well-controlled investigations conducted to evaluate the effectiveness of the drug on the basis of which it could fairly and responsibly be concluded by experts that the drug will have the effect it is purported to have under the conditions of use described in the labeling.

Adequate and well-controlled investigations are further defined in FDA regulations as having various characteristics, one of which is the use of a design that permits a valid comparison with a control to provide a quantitative assessment of drug effect.

It has long been FDA's position that Congress generally intended to require at least two adequate and well-controlled studies, each convincing on its own to establish effectiveness. The usual requirement for more than one adequate and well-controlled investigation reflects the need for independent substantiation of experimental

results.

There may be unanticipated, undetected systematic biases in any clinical trial. These biases may occur despite the best intentions of sponsors and investigators and may lead to flawed conclusions. Independent substantiation protects against the possibility that a chance occurrence of a favorable result in a single study will lead to an erroneous conclusion that a treatment is effective.

There are circumstances in which FDA may rely on something less than at least two adequate and well-controlled studies. In 1997, the FDA Modernization Act, or FDAMA, amended Section 505(b) of the Food, Drug, and Cosmetic Act to make it clear that FDA may consider data from one adequate and well-controlled clinical investigation and confirmatory evidence to constitute substantial evidence, provided that FDA determines that such data and evidence are sufficient to establish effectiveness.

In the 2019 FDA draft guidance demonstrating

substantial evidence of effectiveness for human drug and biological products, further details are provided on the circumstances under which one adequate and well-controlled study plus confirmatory evidence may be capable of providing substantial evidence of effectiveness.

Factors that FDA may consider relevant to such a situation include the persuasiveness of the single trial; the robustness of the confirmatory evidence; the seriousness of the disease and whether there is an unmet need; the size of the patient population; and whether it is ethical and practicable to conduct more than one adequate and well-controlled clinical investigation.

As described in the guidance, confirmatory evidence may include data from adequate and well-controlled clinical studies that demonstrate the effectiveness of the drug in a closely related approved indication; data that provides strong mechanistic support of the drug and the pathophysiology of the disease; data from a well-documented natural history of the disease can

also potentially reinforce very persuasive and compelling results from a single adequate and well-controlled study; and finally, scientific knowledge about the effectiveness of other drugs in the same pharmacological class.

The 2019 guidance provides further details on when a single study alone may be capable of independently providing substantial evidence of effectiveness. In such cases, the large adequate and well-controlled multicenter trial can be considered both scientifically and legally to be, in effect, multiple trials, and can be relied on to provide substantial evidence of effectiveness.

The characteristics of such a trial include the trial is large and multicenter; no single trial site is the main contributor to the observed effect; there are consistent clinically meaningful effects and distinct prospectively specified endpoints; there is consistency of the finding across important patient subgroups; and the design or analysis in the study may allow for multiple comparisons such that there may be multiple studies

contained within a single study. Such characteristics serve to increase the reliability of the reported findings and might allow the results of the single study to provide substantial evidence of effectiveness.

The guidance also states that reliance on a single large multicenter trial to establish effectiveness should generally be limited to situations in which the trial has demonstrated a clinically meaningful and statistically very persuasive effect on mortality, severe or irreversible morbidity or prevention of a disease with potentially serious outcomes, and confirmation of the result in a second trial would be impractical or unethical.

Because of the inherent vulnerabilities involved in reliance on a single study, it is critical that the possibility of an incorrect outcome be considered and that all the available data be examined for their potential to either support or undercut reliance on a single trial.

The statutory standards for effectiveness

apply to drugs developed for ALS just as the standards apply for all drugs of development. However, FDA recognizes that it may be appropriate to exercise regulatory flexibility in applying the statutory standards to drugs intended to treat serious diseases with unmet medical needs while preserving the appropriate assurance of safety and effectiveness.

Much of the discussion today will focus on study conduct issues and detailed statistical considerations of the analyses of the study endpoints. These comments may appear quite technical and perhaps even nitpicky at times, but it is important to recognize that it is the job of the FDA to probe and critically appraise the data to ensure that the quality and robustness of the data are adequate to meet the standards for substantial evidence of effectiveness that I have described.

I would once again like to assure the committee and ALS community that as we conduct our reviews, we continue to keep in mind the context

that ALS is a rare devastating disease with an enormous unmet medical need, however, it is of vital importance and it is legally required for FDA to ensure that drugs are both effective and safe for approval.

The division recognizes that the findings with AMX0035 in ALS appear promising, however, we have considerable concerns that the data may not be sufficiently robust to meet the approval standard for substantial evidence of effectiveness, and that is why we are bringing this application to the committee today. It is also critically important for the committee to consider how the results of the ongoing phase 3 study could potentially impact the assessment of substantial evidence of effectiveness.

Today you will hear presentations from various members of the review team outlining our concerns with this application resulting from the review of the evidence provided by the applicant to support the effectiveness of AMX0035.

Following my remarks, you will hear

presentations from the applicant's team, and you will have a chance to ask clarifying questions. After a short break, we will reconvene with presentations from the FDA. Dr. Emily Freilich, the cross-discipline team leader for this application in the Division of Neurology 1, and Dr. Tristan Massie, the reviewer with the Office of Biostatistics, will provide an overview of the multidisciplinary team's findings and concerns regarding the AMX0035 application. You will again have the chance to ask clarifying questions.

After a break for lunch, we will have the open public hearing followed by discussion and questions to the committee. Again, no final decision has been made on approvability and we very much look forward to the insights you will provide. We have convened this committee because we feel that a final decision requires your input and advice. Thank you for the effort you have made in preparing for and attending this meeting, and thank you for the important work you will do today.

Dr. Montine, thank you for the time to offer

my comments, and I return the proceedings to you.

DR. MONTINE: Thank you, Dr. Buracchio. I will read comments, and then we'll proceed.

Both the FDA and the public believe in a transparent process for information gathering and decision making. To ensure such transparency at the advisory committee meeting, FDA believes that it is important to understand the context of an individual's presentation.

For this reason, FDA encourages all participants, including the applicant's non-employee presenters, to advise the committee of any financial relationships that they may have with the sponsor such as consulting fees, travel expenses, honoraria, and interest in the sponsor, including equity interests and those based upon the outcome of today's meeting.

Likewise, FDA encourages you at the beginning of your presentation to advise the committee if you do not have any such financial relationships. If you choose not to address the issue of financial relationships at the beginning

of your presentation, it will not preclude you from speaking.

We will now proceed with a summary presentation from Amylyx.

Applicant Presentation – Justin Klee

MR. KLEE: Good morning, and thank you all for your time today. My name is Justin Klee, and I'm the co-CEO and co-founder of Amylyx Pharmaceuticals. With me is my fellow co-CEO and co-founder, Joshua Cohen.

Thank you to the chair, members of the panel, and members of the ALS community who have joined to share their perspectives today, and a huge thank you to the thousands of people who have partnered with us to reach this milestone, including hundreds of people with ALS and their families, many of whom are sadly no longer with us. We also want to thank the FDA for inviting us to submit an NDA with priority review and for their consideration of the great unmet need for people with ALS.

The discussion today will center around the

evidence supporting the effectiveness of AMX0035 for the treatment of ALS. The FDA has importantly addressed the context for the discussion and has long stressed the appropriateness of exercising regulatory flexibility in applying the statutory standards to drugs for serious diseases with unmet medical needs.

As we sought to evaluate the potential effectiveness of AMX0035 for the treatment of ALS, we recognized the challenges that face clinical development in a rare, rapidly progressive, fatal disease such as ALS. We therefore sought to partner with leaders in the field of ALS research and clinical trials, the design, conduct, and analysis of the study of AMX0035 in people with ALS. This partnership formed the CENTAUR trial we'll be reviewing with you today.

The CENTAUR trial was conducted through the NEALS at 25 top ALS centers of excellence across the United States, with coordination through the Neurological Clinical Research Institute at Mass General and Outcomes Training and Monitoring

through the center at the Barrow Neurological Institute. The CENTAUR study was designed to be both robust and patient-centric. A 24-week randomized-controlled phase was designed and statistically powered to evaluate functional progression.

An open-label extension was designed to allow for crossover and long-term treatment and to evaluate long-term safety as well as efficacy outcomes on key ALS measures. The trial started in June of 2017, the randomized-controlled phase completed in August of 2019, and the open-label extension completed in March 2021.

The principal investigators of the CENTAUR study are some of the top ALS researchers in the world. Dr. Merit Cudkowicz is the Julieanne Dorn Professor of Neurology at Harvard Medical School and is the chief of neurology at Mass General Hospital. Dr. Cudkowicz served as the co-PI and senior clinical advisor for the CENTAUR study and was integral to all aspects of its design and execution.

Dr. Sabrina Paganoni, who you will hear from today, is an associate professor at Harvard Medical School and the co-director of the MGH Neurological Clinical Research Institute. Dr. Paganoni served as the principal investigator of the CENTAUR study.

The mixed effects model used for the clinical outcomes was developed by Dr. David Schoenfeld, professor emeritus at Harvard Medical School and the most cited statistician in the field of ALS clinical trials.

You will also hear today from Dr. Jeremy Shefner, the Kemper and Ethel Marley Professor and chief of neurology at the Barrow Neurological Institute. Dr. Shefner and his team oversaw the outcomes training and monitoring for the CENTAUR study.

While running clinical trials in ALS is challenging, the design, method, and execution of the CENTAUR study were done in partnership with leaders in the field of ALS research and used the best tools available to ensure a robust and clinically meaningful results. One example of this

is the choice of our primary analysis method.

The FDA raised the use of joint rank as their preferred methodology for this study. While the joint rank analysis can account for deaths, it also has limitations. In 2016 and 2019, we and Dr. Schoenfeld, who is the co-inventor of the joint rank method, wrote to the FDA sharing why the mix effects model was more appropriate as a primary model and, with Dr. Suzanne Hendrix as well, who is here today, we described our proposed sensitivity model to handle deaths. We did not hear back from FDA after our response in 2016, nor our response in 2019, and assumed it was okay to proceed.

I will now turn to my fellow co-founder and co-CEO, Josh, to briefly discuss the results of the CENTAUR study.

Applicant Presentation – Joshua Cohen

MR. COHEN: Thanks, Justin.

The CENTAUR trial met its prespecified primary endpoint, slowing the progression of functional decline, using the most widely used clinical scale in ALS, the ALSFRS-R. We were very

proud to publish with our colleagues the results of the 24-week, randomized phase in the New England Journal of Medicine in September of 2020. AMX0035 also showed a statistically significant benefit in overall survival, extending the lives of those who received AMX0035. This data was published in Muscle & Nerve in October of 2020.

In a disease where neuromuscular degeneration leads to functional loss and death, one would wish to see a slowing of progression that leads to an increase in survival time. This is the first time treatment has shown a benefit on both function and survival in ALS.

AMX0035 showed a good safety profile with numerically fewer serious adverse events in the treatment arm as compared with placebo. While these results are important for people with ALS, it is also important to continue to study AMX0035.

With Dr. Sabrina Paganoni here in the U.S. and Dr. Leonard van den Berg at UMC Utrecht in The Netherlands as co-chairs, we are well underway with recruiting our second placebo-controlled study of

AMX0035 in ALS, the PHOENIX trial. The study has so far recruited 150 participants, and we anticipate top-line results in 2024.

We wish to reassure the panel that we are working hard to complete this study as expeditiously as possible. The study was designed to primarily recruit in Europe, and therefore an approval of AMX0035 in the U.S. will not prevent completion. But we are here today because the FDA invited us to submit an NDA as quickly as possible, recognizing the urgency needed in this terrible disease. The data from CENTAUR supports the case for effectiveness in ALS with a favorable safety profile.

This presentation will focus on the robustness of the CENTAUR study; how the study was designed and conducted; the prespecified primary outcome of function and statistical considerations around its interpretation; the long-term survival benefit; and what these results may mean for people living with this devastating disease. Dr. Shefner and Dr. Paganoni have also joined us today to share

their perspectives.

We have additional experts with us as well today. All outside experts have been compensated for their time preparing for today's meeting. Thank you very much for your time and for the opportunity to introduce ourselves. I'll now turn the presentation over to Dr. Shefner.

Applicant Presentation – Jeremy Shefner

DR. SHEFNER: Good morning. I'm a neurologist and neuromuscular specialist, and I'm chair of neurology at the Barrow Neurological Institute. I've had a long interest in ALS research and clinical care and have been involved in running clinical trials in ALS for more than 30 years. In 1996, I co-founded the NEALS Consortium with Dr. Cudkowicz.

Today I want to talk about several issues related to the design and analysis of ALS clinical trials. As you all know, ALS is a devastating disease for both patients and caregivers to live with. It's also a complex disease to study in clinical trials. Patients are tremendously

variable in the rate with which they progress, which in the past has mandated large trials to maintain sufficient statistical power.

Because of disease progression, trial volunteers have increasing difficulty in traveling to clinical trial sites, and dropouts and deaths and related missing data are a concern. An analysis of over 50 previous ALS clinical trials found that the historical dropout in ALS studies is 22 percent, highlighting the challenge of running clinical trials in a rapidly progressive fatal disease. The dropout rate in the CENTAUR study that we're talking about today is within the range of these previous studies. Finally, we're limited by the fact that there are no validated treatment-sensitive biomarkers.

The ALS investigator community has discussed these issues extensively, both internally and with the FDA. These discussions have led to the publication of the 2019 Airlie House Revised Consensus Guidelines, as well as the FDA ALS guidance for industry, which was also published in

2019. Both of these documents consider the use of specific inclusion criteria to reduce heterogeneity of disease and to decrease the required sample size. These guidelines also note that both function and survival are important endpoints.

When function is assessed, the impact of missing data due to dropout in death should be accounted for. Neither document mandates the use of a specific analysis, as the analysis method depends on the particular study design. The impact of mortality on a functional endpoint can be evaluated as part of the primary analysis or as a sensitivity analysis.

Appropriate inclusion criteria are criteria in ALS clinical trial design to balance the evaluation of function and survival. For example, enrolling participants early in the disease course increases the probability of survival throughout the study. Other criteria contribute to increasing homogeneity of disease progression.

Inclusion criteria in the CENTAUR study mandated a short duration from symptom onset and

the presence of diffuse disease, which prioritized rapid progression but with a high probability to survive the 24-week randomized portion of the study. Investigators were also instructed to only enroll participants they thought would be likely to survive for at least 24 weeks. An open-label extension phase allowed longer term follow-up and evaluation of mortality.

I'd like to talk briefly about how functional measures in ALS are measured and analyzed. The ALS Functional Rating Scale-Revised is the most commonly used outcome for measuring disease progression in ALS trials. This scale assesses for functional domains: bulbar function, fine motor abilities, gross motor abilities, and respiratory function.

Initially in the context of the NEALS Consortium, but now more globally, my group at the Barrow Neurological Institute has developed a training and certification process for both the ALSFRS-R and other outcomes. Both initial and continuing certification are required. This focus

on training and certifications helps to ensure data quality and data consistency. This process was followed for the CENTAUR study.

In clinical trials of ALS, we generally find that the progression of the ALSFRS-R is linear over the course of most clinical trials, and analyses generally assume that progression will be linear unless a prespecified sensitivity analysis finds that this assumption is violated. In the CENTAUR study, the linearity assumption was not violated.

As you'll recall from my recorded presentation, the decline in the ALSFRS-R in both treatment and placebo groups appears linear by inspection. While there is broad agreement that the ALSFRS-R is the appropriate tool to measure function, there are different methods to analyze this, with the overall goal being to appropriately account for missing data or participant deaths.

A shared baseline mixed effect model accomplishes this and is very sensitive to therapeutic response, especially when death is a rare event. In addition to good sensitivity, a

shared baseline mixed effects model effectively handles missing data, allows inclusion of important prognostic covariates, and is a clinically meaningful endpoint used in many recent trials.

The joint rank test is another method that can be utilized in studies and combines the ALSFRS-R and death into one nonparametric statistics. This analysis has been shown to be less sensitive to therapeutic intervention than other models when participant deaths are sparse and is not as effective as the mixed effects model at accounting for missingness due to dropouts or potential baseline imbalances. As discussed above, deaths can also be assessed in sensitivity analyses.

Finally, I want to discuss the standard of care for ALS. There are only two approved treatments, riluzole and edaravone. In the two studies that led to the approval of riluzole, survival was extended approximately 2 to 3 months. The ALSFRS-R had not been developed at the time of this trial, but other functional assessments did

not demonstrate efficacy.

The study, which led to the approval of edaravone, was a 137-patient study run in Japan and showed a 2.5 point benefit on the ALSFRS-R with almost no deaths in the placebo-controlled component of the trial. The associated open-label extension did not report a difference in survival between the two groups. Based on the need to offer standard of care to participants in a trial, as well as the fact that edaravone was approved and launched during the CENTAUR study, the use of either or both agents was allowed during the conduct of this trial.

In summary, disease heterogeneity and dropout rates present challenges in ALS clinical trials. Inclusion criteria can assist in reducing these issues. Similarly, inclusion criteria can maximize patient survival during the randomized follow-up.

When a functional endpoint is employed as primary outcome, statistical analyses to account for missing data due to dropout or mortality should

be employed to evaluate the impact of missing data due to dropouts or death, and the chosen analyses should be appropriate for the study design. Effective use of the ALSFRS-R requires uniform training and certification, and it's imperative that standard of care is provided to all participants in clinical trials.

Thank you. I'll now turn the presentation over to Dr. Timmons.

Applicant Presentation – Jamie Timmons

DR. TIMMONS: Thank you, Dr. Shefner.

I'm Jamie Timmons, head of scientific communications at Amylyx. I'm pleased to be here to share our clinical efficacy and safety results and to highlight the positive benefit-risk of AMX0035. Today I will highlight the fundamental aspects of the CENTAUR trial and clinical data that support the effectiveness of AMX0035.

CENTAUR was a well-designed and well-executed clinical trial. The prespecified primary outcome was met. AMX0035 treatment resulted in a statistically significant and

clinically meaningful 25 percent slowing of disease progression as measured by the gold standard, ALSFRS-R. There was also an ITT overall survival benefit that showed a 4.8-month longer median survival and a 36 percent less risk of death at any specific timepoint in a universally fatal disease.

Importantly, on top of these benefits, AMX0035 was well tolerated with no safety concerns. The evidence supports a positive benefit-risk and shows that AMX0035 would give those living with ALS and their families more valuable time.

Let's start with key aspects of the CENTAUR study design and execution. As Dr. Shefner reviewed, ALS is a complex disease to study in clinical trials. The CENTAUR trial employed a variety of best practices to ensure a quality study. To allow for a sensitive measurement of function, CENTAUR used inclusion criteria to enroll a homogeneously progressing population that would be expected to live through the end of the 6-month randomized-controlled phase.

The gold standard measure for function, the

ALSFRS-R, was used to evaluate the primary endpoint. ALSFRS-R evaluations were completed in a well-established and standardized manner. The ALSFRS-R was analyzed using a shared baseline, linear mixed effects model, which is able to handle missing data and accurately assesses treatment differences in studies with few mortality events like CENTAUR. Prespecified sensitivity analyses were performed to account for missing data due to dropouts and participant deaths. Finally, the benefit of AMX0035 was tested on top of standard of care, riluzole and edaravone.

The CENTAUR study began in June of 2017 and was conducted in 25 centers around the United States with two phases, a randomized-controlled phase and an open-label phase. 137 participants were randomized 2 to 1 to receive AMX0035 plus standard of care or placebo plus standard of care, respectively. Participants who completed the randomized-controlled phase on study drug were allowed to enter the open-label phase and receive AMX0035. Investigators and participants were

blinded to study treatment throughout CENTAUR.

The open-label phase ended on March 1, 2021, as the number of participants remaining in the study were less than 20, and it was growing increasingly complex to monitor participants due to the COVID-19 pandemic. Remaining participants were transitioned to an extended-use protocol.

At the beginning of CENTAUR, a randomization implementation problem was identified and addressed by the unblind statistician. Participants, investigators, and study staff were never unblinded to this error, and after the correction, the 2 to 1 active-to-placebo ratio was maintained.

The impact of this error was assessed by a sensitivity analysis that excluded affected participants. The results of the sensitivity analysis were similar to the prespecified primary analysis shown at the top of this figure, confirming that this early randomization implementation error did not impact the primary results. It's important to consider any factors that could lead to unblinding in any study. All

available evidence indicates that participants and investigators remained blinded throughout the CENTAUR study.

AMX0035 has a bitter taste. Placebo was carefully taste matched in the study and included a bittering agent. AMX0035 can also cause GI adverse events. While there are some differences in the incidence of types of GI adverse events between groups, the differences were small, events were generally mild or moderate, and the overall incidence of GI adverse events was similar between the AMX0035 and placebo groups, 66 percent and 63 percent, respectively.

Based on an exit questionnaire performed at the end of the randomized phase, it asked investigators and participants what treatment arm they were assigned to. Neither study investigators nor participants were able to guess treatment assignment. The active group was not able to guess their treatment assignment any better than chance, indicating that taste and GI adverse events were not leading to unblinding.

Finally, as stated earlier, the blinded to original treatment assignment was maintained throughout the entirety of both the randomized and open-label phases. Sites were emailed unblinded treatment information on October 15, 2021, well after the last participant last visit of the open-label phase March 2021.

As Dr. Shefner reviewed, there are different acceptable methods to analyze the ALSFRS-R. There is not a one-size-fits-all model, and ALS clinical trials adjust the analysis approach based on study design and objectives. The shared baseline linear mixed effects model used in CENTAUR was an appropriate model for this study. One consideration that led to this choice was the expectation of a limited number of deaths during the randomized-controlled phase, and this is what we saw. There were few deaths during the randomized-controlled phase, 6 percent in the AMX0035 group and 4 percent in the placebo group.

The shared baseline linear mixed effects model used in CENTAUR provided a precise estimate

of the treatment effect; counted for missing data due to participant dropout; allowed inclusion of important prognostic covariates; and yielded a clinically meaningful result. Additionally, prespecified sensitivity analyses were performed to account for missing data due to dropouts and participant deaths.

Now turning to the primary endpoint results, prespecified primary endpoint was met in the randomized-controlled phase. Participants treated with AMX0035 showed a statistically significant slowing of functional decline compared to placebo.

The group separated at a rate of 0.42 points per month, which represents a 25 percent slower decline in function for AMX0035 compared to placebo. Importantly, this separation began at week 6 and was sustained to week 24. This effect was seen on top of standard of care riluzole and edaravone. At the end of the randomized-controlled phase, this slowing of functional decline in the group treated with AMX0035 resulted in a 2.32 point benefit on the ALSFRS-R scale.

We can evaluate the robustness of the primary endpoint against a number of assumptions, including shared baseline linearity, the impact of missing data due to dropout or participant deaths, and the impacts of concomitant medications. I walked through these different analyses in detail in the recorded presentations, and I'd like to highlight a few of them today, as they address specific points raised by the FDA.

First is the assumption of linearity. The statistical analysis plan prespecified criteria under which the quadratic model would be used. Those criteria were not met, so the linear model was appropriately used. However, it's perhaps a bit more intuitive to take a step away from the linear versus quadratic discussion and look at the highlighted sensitivity model, a traditional mixed model with separate means by visit. This model has no assumption of linearity or of a shared baseline and is consistent with the primary results.

The impacts of participant death on the primary outcome can be assessed using different

methods, the joint rank analysis shown on the next slide and by assigning a worst-case value for the ALSFRS-R, highlighted here. The prespecified left-censored analysis, which adjusts the ALSFRS-R towards a worse outcome for participants who died, and the post hoc worst-case imputation of an ALSFRS-R of zero were both consistent with the primary results.

As noted, most participants in the study were taking riluzole or edaravone at baseline. In uncommon cases, participants did initiate these drugs during the study. Results shown here are from a prespecified analysis using a time-dependent covariate and show that the beneficial effect of AMX0035 on the ALSFRS-R was consistent after adjusting for time on each medication during the randomized-controlled phase.

Regardless of the assumption tested, the effect size of AMX0035 on the ALSFRS-R remains generally consistent, between 1.9 to 2.9 points, highlighting the robustness of the prespecified primary endpoint results.

FDA rates joint rank specifically, so let's look at that next. Shown here are three joint rank analyses using different populations, mITT or ITT, and different assumptions to account for missing ALSFRS-R data. As a reminder, there were a limited number of deaths in the randomized-controlled phase, and they were balanced between groups. These post hoc analyses were consistent with the results of the prespecified primary efficacy analysis and, again, indicate that the primary outcome results are unaffected by including death in the model.

Next, the time-to-event results, including ITT overall survival, the time-to-event endpoints, including overall survival, use a cutoff date of March 1, 2021, which corresponds to the overall last participant last visit in the study. Time-to-event analyses compared all participants originally randomized to AMX0035 versus those originally randomized to placebo. The prespecified time-to-event composite endpoint was the time to death; overall survival; first hospitalization and

death equivalent; tracheostomy; and permanent assisted ventilation.

Data on hospitalizations and death equivalent events were collected systematically via clinic visits for participants in the open-label phase but may not have been collected after dropout. As such, there is some risk of missing data when hospitalization and death equivalent events are included in the composite analysis.

The prespecified composite time-to-event outcome was met. As of March 1, 2021, 112 events were captured. That's 82 percent of randomized participants with an event. There was a statistically significant 4.8-month median difference in time to death, first hospitalization, or tracheostomy and permanent assisted ventilation in the group originally randomized to AMX0035 compared to the group originally randomized to placebo. The hazard ratio was 0.62 and the p-value was 0.023.

Overall incidence of tracheostomy and permanent assisted ventilation was low. Only one

participant underwent tracheostomy and initiated permanent assisted ventilation in the randomized-controlled phase, 3 participants underwent tracheostomy, and 10 participants initiated permanent assisted ventilation in the open-label phase.

As mentioned earlier, the composite time-to-event outcome has the potential for missing data due to the inability to capture hospitalizations and death equivalent data after dropout. However, the individual overall survival outcome does not have the risk of missing data, as it was possible to capture vital status using both clinic visits and public records.

Vital status for all but one originally randomized participant, 136 out of 137, was captured for the overall survival part of the composite outcome. The one participant not captured as of the cutoff date is censored as of their last clinic consult [indiscernible]. Survival status was confirmed even on those participants who dropped out of the study through

an evaluation of public records, including the Social Security Death Index.

Since missing data is not an issue in the overall survival part of the composite outcome, it is informative to look at these individual results in depth. Let's review the overall survival results first in the mITT population.

AMX0035 results in an overall survival benefit in the mITT population, showing a significant median survival difference with a hazard ratio of 0.61. While the statistical analysis plan prespecified the mITT population for efficacy outcomes, the ITT population is often considered the most robust population to use for survival outcomes, so let's look at those results now.

Recall that this overall survival analysis has essentially no missing data. In this comprehensive analysis, we see a statistically significant median survival difference of 4.8 months between those participants originally randomized to AMX0035 compared to those originally

randomized to placebo and 36 percent less risk of deaths at any specific timepoint on top of standard of care.

At the time of the March 1, 2021 data cutoff, 94 deaths had occurred, representing nearly 70 percent of randomized participants. The data shown align to our prespecified model for survival outcomes. Put simply, in a rapidly progressing and universally fatal disease, death is the most definitive outcome, and here we see a significant difference between people randomized to AMX0035 to those randomized to placebo.

Composite and individual overall survival outcomes were assessed at three timepoints over long-term follow-up using the comprehensive survival data capture method, February 2020, July 2020, and March 2021. Let's walk through the rationale for each of those cutoffs.

February 2020 corresponds to the initial comprehensive longer term survival evaluation after the randomized-controlled phase. This was performed in relation to a March 2020 Type C

meeting with the FDA. In July 2020, the longest follow-up was 3 years post-randomization, and approximately 50 percent of participants had died. An interim analysis from this cutoff showing a median survival benefit of 6.5 months was published in Muscle & Nerve.

March 2021 corresponds to the last participant last visit in the open-label phase and was requested by the FDA and recommended as the key timepoint for analysis for benefit-risk. The long-term follow-up statistical analysis plan, signed off prior to unbinding, also specifies that the composite time-to-event endpoint would be assessed at the end of the study, so this is the mean analysis for survival. Regardless of cutoff date, the survival benefit for AMX0035 was consistent, showing a hazard ratio between 0.57 and 0.64.

Next, a brief review on the safety and tolerability of AMX0035 in the CENTAUR study. Adverse events and deaths were balanced between the treatment and placebo arms. While GI events with AMX0035 occurred more frequently in the first

3 weeks of treatment, they generally tapered off to the same level as placebo throughout the rest of the study.

There were fewer serious adverse events with AMX0035, and most were related to ALS progression. More adverse events that led to drug withdrawal in the AMX0035 group were related to gastrointestinal symptoms. Overall, AMX0035 was well tolerated with no safety concerns.

Moving now to the final assessment of benefit-risk, to close, the evidence supports a positive benefit-risk for AMX0035. There is evidence of efficacy on function and survival on top of standard of care in a rare and rapidly fatal disease with high unmet need. Most notably, the prespecified primary outcome was met. Both our and FDA sensitivity analyses confirm the same thing, general consistency of the results regardless of the assumptions tested, and AMX0035 was generally safe and well tolerated in the CENTAUR study.

I'll now turn to Dr. Paganoni to present her clinical perspective.

Applicant Presentation – Sabrina Paganoni

DR. PAGANONI: Thank you, Dr. Timmons.

My name is Sabrina Paganoni, and I am the co-director of the Neurological Clinical Research Institute at Mass General. I'm also a physician scientist at the Healey & AMG Center for ALS, and an associate professor at Harvard Medical School.

I served as the principal investigator of the AMX0035 CENTAUR trial, and I'm also the co-chair of the steering committee of the ongoing phase 3 trial. I'll try to close the presentation by sharing my clinical perspective on the data that you've seen today.

ALS is an awful disease. By the time I diagnose someone with ALS in my clinic, the ALS clock has been ticking for months, and their life expectancy is only about two years. Patients, their family, and I know that they are destined to rapidly lose muscle strength and function.

Every time I see one of my patients in clinic, I see the impact of this loss. I see my patients go from walking on their own, using a

cane, to using a wheelchair; from breathing on their own, to requiring a BiPap meeting with hospice. Patients tell us that they want to retain their independence, but once the function is lost, it will not be regained. This is why it's important that we start treatment as early as possible to try to preserve the remaining motor neurons and in turn prolong functional independence and survival for as long as possible, and with AMX0035, we see both.

I know that today's meeting materials contain a lot of details of the nuances of the statistical models, and I know that different statisticians have different opinions. But at the end of the day, we are talking about the lives of people who have a rapidly progressing and fatal disease.

I know that this drug does not stop or reverse the disease -- nothing does -- but we see a positive impact on both function and survival, and these results are valid. The active and placebo arms were well-balanced, meaning that this was a

homogeneous CENTAUR group of people who were predicted to have similar outcomes. But when we looked at their outcomes after 6 months, the participants randomized to AMX0035 had a 25 percent slowing of disease progression, which means that people retained physical function for longer.

While the secondary endpoints did not reach statistical significance, the results of muscle strength and respiratory capacity were consistent in favor of the active arm, and we know that the measures of muscle strength and respiratory function are limited by potential variability of these measures. This is why the study was powered on the primary outcome or the ALSFRS-R, which had a positive result on the prespecified analysis.

Importantly, participants who were originally randomized to AMX0035 lived about 5 months longer than people who started on placebo. Of note, we captured vital status, meaning whether the patients were dead or alive, on all but one participant, and the survival analysis was a randomized analysis because we compared the entire

group that started on active drug to the entire group randomized to placebo.

The impact of AMX0035 on death alone for the composite of death, tracheostomy, and hospitalization was similar. In the U.S., only 5 percent of ALS patients choose to receive a tracheostomy, and this practice is consistent across enrolling sites, which were all in the U.S., so the number of tracheostomy events was quite small. There was consistency in the treatment effect size on the key clinical outcomes of function and survival, and these results were seen on top of standard of care.

In a rapidly progressing and universally fatal disease, treatment effects of this magnitude are clinically meaningful and are comparable or better to the already approved treatment for ALS. In fact, this is the first time that we have seen a benefit in both function and survival in an ALS clinical trial.

As you have seen from the more than 500 comments that have been submitted in response

to today's meeting, slowing of disease progression and longer survival are the outcomes that matter to people with ALS. As my patients tell me, longer survival could mean being able to attend their child's graduation or take a last family trip.

The choice that is in front of us today is this. Should AMX0035 be approved now to benefit people who need better options? Amylyx is already conducting a phase 3 trial, mostly in Europe, that will supplement the data that we are discussing today. The trial is already up and running, and approval of AMX0035 in the U.S. now will not have a negative effect on the ability to complete the European phase 3 trial.

On the other hand, delaying the approval of AMX0035 in the U.S. until we have the phase 3 trial data means that U.S. patients, people living with a rapidly debilitating and fatal disease, will have to wait at least two to three years to get access to a treatment that has shown a benefit with a good safety profile.

ALS is a complex disease. If we look at the

history of drug development in HIV and MS, we know that the first treatments that were developed for these diseases, they were not curative, but these treatments started to buy time for patients.

We're still in the early stages of ALS drug development. As physician investigators, we need to continue to develop more and more effective treatments, including treatment for sporadic ALS and targeted treatments. But as we do so, it is imperative that we use a patient-centric approach. People deserve more function and more time, and here we have a drug with an acceptable safety profile.

This is, after all, a question of benefit and risk. Based on the strength of the current efficacy data, the benefit of AMX0035 is clear. Based on the favorable safety profile, the risk of AMX0035 is low. To me, the greatest risk comes from delaying access to a treatment that has demonstrated a significant benefit. If access is delayed, the patients I see in my clinic today may never receive the time and function that they could

have had. Delaying access is not a risk that we should take.

Thank you for your attention. I will now turn the presentation back to Dr. Timmons to address your questions.

Clarifying Questions to the Applicant

DR. MONTINE: Hello, and thank you to all the speakers from Amylyx. We will now enter our session where we take clarifying questions.

A few rules of the road to handle the awkwardness of doing this by teleconference, please press the hand icon to raise your hand if you wish to be acknowledged to speak. When I acknowledge you, please state your name for the record, and if possible, direct your question to a specific speaker, or if it concerns a particular slide in the presentation, if you can, refer to the slide number.

After you have had your turn to speak and ask questions or make comments, please signal when you're done either by simply saying, "Thank you" or "That's all for my questions," and then I'll know

that we're ready to move on to the next panel member. Then finally, when you're done, please push the hand icon again to lower your hand.

Let me see here.

Jessica, can I ask you, are we scheduled to take a break now or we're going to proceed with the questions now?

DR. SEO: Yes, Dr. Montine. We'll proceed with the clarifying questions for Amylyx for 30 minutes.

DR. MONTINE: Great. Thank you. My apologies. I will start by just working down the list as I see it.

Dr. Nath, would you please take the floor?

DR. NATH: Yes. Thank you very much. This question is for the investigators. First, I want to thank them for providing a very comprehensive review and very detailed review of the study.

I was wondering in addition to the parameters that they presented here, did they also measure cognitive function in these patients, and what about p75 in the neurofilament light chain,

which is other things that are commonly done in ALS studies? Also, how did they measure compliance with the medication? Were drug levels measured in these patients or not?

DR. TIMMONS: Dr. Paganoni?

DR. PAGANONI: I'll start. Thank you for your question, Dr. Nath. Compliance was very high and was measured by measuring essentially the returned sachets. The compound comes in sachets, and so that was done systematically at the study sites.

In terms of your other questions on outcomes, we did not measure cognitive function or p75. We did get plasma samples and measure neurofilament levels, heavy chain.

DR. NATH: Well, why not light chain? Did you measure light chain also or not?

DR. PAGANONI: We did have plasma samples, and ultimately measured also neurofilament. The decision to start with heavy was because when we started the trial, when we planned the trial in 2015-2016, we had a lot of data on neurofilament

light in the field, so that's why we went with that first.

DR. NATH: So you have data on neurofilament light or you don't have data on neurofilament light to share with us?

DR. TIMMONS: This is Dr. Timmons from Amylyx. We do have data on neurofilament light. Similar to what we see with neurofilament heavy chain, we do not see a difference between the placebo and AMX0035 groups.

DR. NATH: Alright. Thank you.

DR. MONTINE: Thank you, Dr. Nath. If that's the end of your comments and questions, could you please lower your hand? I'll just give you a moment.

Great. Thank you.

Dr. Follmann, would you please take the floor?

DR. FOLLMANN: Yes. Thank you. This is Dean Follmann from NIH. I have four questions. I don't know if I should ask them all now or wait, but let me start with the first two. These relate

to slide SP-28 and SP-29, where you go into the details of some of the sensitivity analyses that you did. I had two questions.

For death, you have an analysis at so-called left censored. Could you give you more details about that?

DR. TIMMONS: Dr. Hendrix?

DR. HENDRIX: Good morning. This is Dr. Suzanne Hendrix, and I've worked in clinical trials for over 30 years, and I've specialized in neurodegeneration for the past 19 years, particularly because of the challenges inherent in this field and inherent in the measurement of neurodegenerative outcomes.

As far as your question, the left-censored analysis was essentially taking each person who died and taking their last value, and then computing a distribution of scores below that value, and then imputing that several times and averaging across those for the analysis. So it's a multiple imputation method that uses a distribution of worst-case scores based on the person's last

observed value.

DR. FOLLMANN: So if they died at, say, week 12, and there were like three or four additional measurements that would have been taken [indiscernible] had they stayed alive, you would impute three or four additional measurements?

DR. HENDRIX: At the point that they died, we would take their last value observed and then impute several measurements below that, and then take the average of that distribution of scores into the multiple imputation summary.

DR. FOLLMANN: But that was for future follow-up times? I mean, you have their score just before they died. You just do an imputation -- you have multiple visits after they pass away --

DR. HENDRIX: Yes.

DR. FOLLMANN: -- and did you impute values for the multiple visits?

DR. HENDRIX: I understand your question. So we imputed only the next scheduled visit using this left-censored distribution for them.

DR. FOLLMANN: I see. So it's just one

additional imputation; not sort of filling out the complete trajectory of follow-ups, which I guess you didn't do. Then I guess it's similar for death, where you just say, ok, this person died before, say, week 12, so we imputed 0.12, and then you have the missing at random assumption I guess applying after that?

DR. HENDRIX: That's correct, although I would like to point out that our primary prespecified model used the linearity assumption. So for each individual, the line was fit with all available data, and then that primary analysis took into account that slope per person and combined it in the overall model so that at the time they dropped out or died, that final value pulls that slope down, and then that's used in the model.

DR. FOLLMANN: Okay. Thanks.

My next question has to do with SP-29 where you talk about a joint rank analysis. I have an idea what that probably is, but I'm not sure, and probably the committee doesn't as well; so if you could just briefly explain how you rank.

DR. HENDRIX: Yes. Suzanne Hendrix again. The goal of the joint rank analysis is to make sure that we don't have more deaths in the active arm that are then causing it to look like we have a functional benefit with the participants who are remaining.

The way the joint rank works is it ranks every individual score for everyone who has the ALSFRS-R, and then those participants who died are ranked as a worst case with the earlier deaths getting the lowest ranks and later deaths getting the next higher ranks until the last participant who died gets this bottom block of ranks. So all the deaths are at the very bottom, everyone who's still alive is at the top, and then the missing data is between those two values.

We have three different versions of this model here. The first one is taking the last observed time for each individual, and then ranking those scores, and then analyzing those in the next model. The second one that's shown here uses multiple imputation, imputes data to the end of the

study for all participants, but then to rank those imputed scores at the 24-week timepoint, and then that analysis is the middle group.

The last one shown here is the same thing as the second, but then we're also using in addition to death the additional outcomes that were part of our composite as one of the reasons for ranking at the lowest case; so then we are analyzing each of those with these ranks.

Now, there are two things that the joint rank model does. Number one, as I mentioned, it accounts for the deaths and it gives them a worst-case outcome. But number two is it loses the scale that we started with, so the ALSFRS-R points are no longer visible in the scale, and instead we have a ranked point value here that's the number of ranks different the groups are. By doing the ranking, we do lose some information of the original scale, and we do that in order to accommodate including the death in that analysis.

DR. FOLLMANN: Thank you.

I have a couple other questions. I think

the next one should be for you as well.

In the briefing materials, there was a table that showed the slope of decline during the blinded phase for the two arms and then also the slope of decline for the open-label phase for the two arms when both are on drug now.

I was wondering if you had that table with confidence intervals for it because I'd like to gauge the evidence for a drug effect in the placebo crossovers, and you have a point estimate that's no uncertainty about it.

DR. HENDRIX: These estimates are just point estimates and were not calculated with confidence intervals around them, but that's something we can get for you after the break.

DR. FOLLMANN: Thanks.

Then the final question is related to the PHOENIX study. I'm interested in the rationale for it and maybe a little more about the design. For example, that's a study of 600 patients rather than this study was 137. Were there different design considerations?

So that's one thing, a little more about the details of that, and then what was the rationale for doing this study? Is it to get, I guess, licensure in Europe or what?

DR. TIMMONS: This is Dr. Timmons from a Amylyx. I'll address this question.

In terms of the PHOENIX study design, there are some similarities between the CENTAUR trial, but there are some key differences that require the adjustment of the study design. In terms of the sample size, we are looking at a more heterogeneous population in the PHOENIX study, and as mentioned, the CENTAUR study was a homogeneously progressing patient population, especially due to the inclusion criteria of definite ALS and also restricting to less than 18 months from symptom onset.

As you can see here on the PHOENIX study design, it is a broader inclusion criteria, definite clinically probable ALS and less than 24 months from symptom onset. In addition, we will be able to answer some key questions in PHOENIX that we're not able to answer in CENTAUR,

specifically being able to stratify by edaravone use.

In terms of the question for why conducting the study, there are certainly a few. Namely, as we mentioned, the majority of participants are in Europe, and a year-long study is necessary for approval in the EMA. As mentioned in the FDA's introduction, based on our back and forth, this study was also to include U.S. participants, which it does, in addition to provide more data before the decision was made to submit the NDA.

DR. FOLLMANN: Thanks, and just one final question. What's the primary endpoint for those?

DR. TIMMONS: The statistical analysis plan is not finalized yet, so we don't have the specific analysis yet, but it will be a combined assessment of function and survival, change from baseline in ALSFRS-R, and survival at 48 weeks. We will be working through the exact method to perform that analysis.

DR. FOLLMANN: Thank you. That's all I have. Over.

DR. MONTINE: Thank you, Dr. Follmann.

Next on the list is Dr. Caleb Alexander. If you would, please?

DR. C. ALEXANDER: Sure. This is Caleb Alexander. I think this is for Justin Klee.

You noted that in referring to the method of modeling the primary outcome, you noted, "We didn't hear back from the FDA in 2016 or 2019 and assumed it was okay to proceed."

This is one of several important differences, I believe, between the sponsor and the FDA's approach to the matter, so I just wanted to be clear whether this is to suggest that you weren't aware of the FDA's concerns about modeling the primary outcome the way that you did until CENTAUR was underway. And if that's the case, had you have been aware, what would you have done differently?

DR. TIMMONS: Justin Klee?

MR. KLEE: Hi. Justin Klee here. No, we were aware of the FDA's preferred methodology. They brought it up in the pre-IND meeting that they

would prefer a joint rank analysis of function and mortality. We wrote back, along with Dr. Schoenfeld, who, as I mentioned, is the co-inventor of the joint rank method, and Dr. Schoenfeld strongly encouraged both us and the FDA that he thought a mixed effects model would be more appropriate for this study design, given the inclusion criteria and given the expectation that there would be few mortality events in the 24-week randomized study.

So when I was referring to our conversations, we wrote back after the 2016 pre-IND discussion, and we did not hear after that. We submitted the statistical analysis plan in 2019. We received comments again suggesting the use of joint rank. We wrote back again with our proposed sensitivity analyses, but keeping the primary given that the study had been powered and was well underway at that point on that outcome.

So I hope that clarifies.

DR. C. ALEXANDER: Yes, that's helpful. I know and appreciated seeing the sensitivity

analyses that were done, so I imagine for one of your colleagues just a question about that.

My understanding is that the approach that you used to manage missing data in the sensitivity analyses using the log-rank test was the last observation carried forward approach, which as you know requires very strong assumptions that on their face would seem to be problematic in a disease such as ALS. So I wondered if someone could speak to that.

DR. TIMMONS: This is Dr. Timmons from Amylyx. I'll start showing the slide here that shows the different joint rank analyses. The analysis you're referring to is in the top row, and then analyses using a multiple imputation method are row 2 and 3, and I'll have Dr. Hendrix walk us through.

DR. HENDRIX: Dr. Hendrix.

On the first analysis, it did use the last available data for deriving the rank, and the main reason for that was we were reading the publication that described the joint rank model that the FDA

had forwarded to us, and we were trying to mirror what was in that the closest we could according to what they had in there, and then we performed this analysis following that direction.

The publication itself is not completely explicit about the algorithm, and rereading it, there's some ambiguity of how exactly it would be interpreted. So these additional analyses are including some of those other ways to do it, but of course they also bring in the multiple imputation, which brings in additional variability into that modeling.

As I mentioned earlier, I think remembering the goal of the joint rank, which is to make sure that the deaths are not making it look like function is better than it really is, in this case where we actually have a survival benefit based on the long-term data, there's really little concern that the deaths are going in the wrong direction, and in this short amount of time of the 24 weeks, we're not necessarily able to see that.

So we feel like the analyses that we did

using an imputed value of zero or 7 for the deaths are maybe a more appropriate way to look at this without losing power from the joint rank by doing the ranking, and also without losing power due to the multiple imputation.

What we find is that whichever way we do this, with the zero imputation, with the 7, with all three of these different methods here, multiple imputation or doing the last observation carried forward, the results are extremely consistent with effect sizes close to 2 to 2 and a half on the ALSFRS-R, rank scores between 12 and 14, and then consistent statistical evidence across all of those approaches.

DR. C. ALEXANDER: Thank you.

The final question has to do with -- if it's true -- really remarkable survival benefits that are suggested by the open-label analyses. I just wondered that given what you describe, as well, as robust and sustained slowing in functional decline that begins very early in the randomization phase of the trial, why you believe that there were no

statistically significant benefits with secondary endpoints.

I know that you spoke to muscle strength, but it's not just one secondary endpoint, it's muscle strength, it's biomarkers, it's respiratory capacity, and perhaps most puzzling, composite survival. So what do you think accounts for the discrepancy and the discordance between the really remarkable gains that appear if you take the open-label results on their face and the analyses during the randomized portion of the study?

DR. TIMMONS: Dr. Shefner?

DR. SHEFNER: Jeremy Shefner. Well, I think this is a simple answer, and that's that there were essentially almost no deaths during the 24-week randomized, placebo-controlled portion. And the reason that there were almost no deaths was that the inclusion criteria prioritized people who would likely survive that 24-week period.

So I think that really accounts for discordance. You are able to see functional endpoints but aren't going to see a survival impact

if survival is nearly uniform.

DR. C. ALEXANDER: But if I'm understanding what was reported in the New England Journal of Medicine report, as well as what we've heard thus far, there were no statistically significant effects on any of the secondary endpoints; so muscle strength or respiratory capacity either.

DR. SHEFNER: Sorry about that. I misunderstood the question.

The impacts are not statistically significant, but in terms of point estimate of effect, they're very similar to the impact on the ALSFRS-R. So I think just in terms of the characteristic of these outcome measures in this and other studies, the variability of measurement is somewhat in excess of the ALSFRS-R. So the similar point estimate of effects are going to be less significant, and this is consistent with multiple other previous trials.

DR. C. ALEXANDER: Thank you.

DR. MONTINE: Thank you.

Dr. Fischbeck, would you please?

DR. FISCHBECK: Sure. This is Kenneth Fischbeck at the NIH. I have several questions, three or four questions, if there's time, but I'll maybe just ask one to start with primarily for Joshua Cohen, I guess, but others can chime in, about the PHOENIX study, the status of the phase 3 study.

Clinicaltrials.gov doesn't list any of the European sites. It just lists 33 sites in the U.S., and only two or three of them are listed as recruiting. The Dallas site is listed both as recruiting and not recruiting.

I wonder if the FDA approves this application, what will happen to the PHOENIX study, and in particular the PHOENIX study in the U.S. Will that be discontinued? Will it be continued? Where is it now, and what are your plans for it if you get approval?

It seems if you get approval and start to market the drug in the U.S., some of the money you may have set aside for this study could be available for other things. I wonder if you're

willing to pass it back to the patients with an affordable limit on the price of the drug.

DR. TIMMONS: Great. To start with the first part of the question in terms of, just in general, the PHOENIX sites, I can show those up for you real quick here.

DR. FISCHBECK: Who is it who's speaking?

DR. TIMMONS: I'm sorry. Apologies for that. This is Dr. Timmons from Amylyx.

DR. FISCHBECK: Yes. I directed the question to Joshua Cohen.

DR. TIMMONS: Absolutely.

Joshua Cohen?

MR. COHEN: Hi. This is Josh. Yes, it's a great question. We designed the study very much so to be able to complete regardless of the ultimate decision on this NDA, and that's very much our commitment. We believe it's really important to continue generating data in ALS, and that's why we're doing that.

In terms of the U.S. sites, we've been quite thoughtful about that, and we also want to ensure

that we don't have too much truncation of data on patients. So actually, currently we have basically stopped our recruitment in the U.S. and are continuing our recruitment in Europe given the current status of the NDA and how close the PDUFA date is. But regardless, in Europe we are very confident that we'll be able to complete the study and that we have enough sites.

Let me try to put this up. Did this go up; the European sites? Nice.

I'm surprised they're not updated on clinicaltrials.gov; we can certainly update that. But we have quite a number of sites in Europe as well.

DR. MONTINE: Great. This is Tom Montine.

If I may, Dr. Fischbeck, I'll circle back to you. Time is starting to be short, and I want to be sure we give everybody a chance.

DR. FISCHBECK: Okay.

DR. MONTINE: Dr. Apostolova, please?

DR. APOSTOLOVA: Yes. This is Liana Apostolova from Indiana University. I have a

couple of questions, one for Dr. Paganoni and the other one for Dr. Hendrix, perhaps, or the CEOs.

Dr. Paganoni, the FTD subtype of ALS is known to carry even poorer prognosis than ALS by itself. Was an FTD subtype excluded by the exclusion criteria or, alternatively, were the groups balanced based on executive dysfunction at the start of the study?

DR. TIMMONS: Dr. Paganoni?

DR. PAGANONI: Thank you for your question. No. Based on the exclusion criteria, the CENTAUR trial excluded patients who had the presence of significant cognitive impairment or dementia, so patients with FTD were excluded.

DR. APOSTOLOVA: And the executive dysfunction wasn't measured and compared for baseline between the two treatment groups?

DR. PAGANONI: No, it was not formally measured. In terms of the exclusionary criteria, that was left to the clinical judgment of the site investigator to only enroll people that didn't have cognitive impairment.

DR. APOSTOLOVA: Okay. Thank you.

The second one has to do with the survival analysis. I believe in the preview materials, it was mentioned that maybe the two groups, treatment versus placebo, had a different percentage of individuals starting edaravone during the trial after randomization. Was that adjusted for?

DR. TIMMONS: Dr. Hendrix?

DR. HENDRIX: This analysis was not adjusted for use of edaravone, but if you recall, the number of patients who started on edaravone was 4 percent in the placebo arm and 12 percent in the active arm. And on this plot that shows the survival, you see that that 6-month time period in which they started, it's just the very beginning of this curve, and the separation that we're seeing is throughout the entire curve. When we do adjust the ALSFRS-R functional outcome for use of edaravone, or riluzole, or both together, we get very similar results at two different ways.

Let me show now then post hoc Cox regression, or I'll mention the post hoc Cox

regression model where we did adjust for baseline use of edaravone. Instead of the hazard ratio of 0.62, which means you have 62 percent of the risk at any timepoint, in the treated patients compared to the overall patients, we instead have a risk of 0.57, so 57 percent of the risk of the placebo group and the active group. So when we adjust for edaravone, we actually get a slightly better hazard ratio than we do if we don't adjust.

DR. APOSTOLOVA: Thank you. I have no further questions.

DR. MONTINE: Thank you.

Mr. Weston, please?

MR. WESTON: Yes. Thank you. I'm going to go in a slightly different direction.

At the outset, I believe it was Mr. Cohen who mentioned that each of the Amylyx presenter team members were being compensated with respect to their preparation for the meeting, and I want to dig just a little deeper on that and ask each of you, in addition to being compensated for preparing and presumably appearing at this meeting, do any of

you have ongoing financial interests in a positive outcome of this drug application such as an equity interest in the company or something similar?

Thank you. I'll mute myself. That was my question.

DR. TIMMONS: This is Dr. Jamie Timmons. I am an Amylyx employee. I'll have Dr. Paganoni come up next.

DR. PAGANONI: Hi. This is Dr. Paganoni. I don't have any equity in the company. I have received research grants as the PI of the CENTAUR trial and as a co-chair of the ongoing PHOENIX phase 3 trial, and I've had institutional consulting agreements, again, to compensate for my work for these trials.

DR. SHEFNER: Hi. This is Jeremy Shefner. I have served on a couple of Amylyx sponsored advisory panels for which I've received consulting income. I have no equity interest, but I have received research support for managing the components of the CENTAUR trial that were previously discussed.

DR. HENDRIX: Dr. Suzanne Hendrix. My company that I'm full owner of has been contracted to do the statistical analysis of this study, and then I've been contracted with consulting around this meeting. I have no equity interest in anything associated with the Amylyx.

DR. TIMMONS: Those are the core presenters besides Joshua Cohen and Justin Klee, who are the co-CEOs of Amylyx.

DR. MONTINE: Thank you.

Dr. Robert Alexander, please?

DR. R. ALEXANDER: Thanks, Dr. Montine.

This is Robert Alexander. I have a couple questions for the sponsor.

First, outside of the clinical data that was presented, is there evidence that the component drugs in AMX enter the brain, and in particular, do you have any estimation of the brain exposure relative to the exposures where effects were seen in preclinical models?

My second question, if you have the baseline levels of the phosphorylated neurofilament heavy in

the two groups in the randomized period, if you could share that. Thanks.

DR. TIMMONS: In terms of the first question, do we have any data in CSF in the brain, in the ALS clinical trial, we did not collect CSF samples, only plasma. In our Alzheimer's clinical study, we were able to collect CSF, and we do see evidence of impact on key biomarkers there: phospho-Tau, PHOTAU, and the Abeta 42/40 ratio.

I think the next question was to show the baseline neurofilament levels, which I can pull up for you here.

DR. R. ALEXANDER: Yes, if you have them, that will be great.

DR. MONTINE: I'm sorry to interrupt. We've run out of time in this session. There will be time for further clarifying questions later in the day. So since you have the slide up, would you please just briefly run through this, and then we'll adjourn for a break?

DR. TIMMONS: Yes, absolutely. This is Dr. Timmons. The baseline neurofilament levels

were balanced between groups. The difference that you see here, there's no significant difference between the AMX0035 and placebo group.

DR. MONTINE: Thank you, and I apologize for interrupting.

We're now going to take a 10-minute break. Panel members, please remember there should be no communication, no chatting, and no discussion of the meeting topics or with other panel members while we're taking a break. We're going to reconvene at 11:55 Eastern Time Thank you, everyone.

(Whereupon, at 11:47 a.m., a recess was taken.)

DR. MONTINE: This is Tom Montine. Welcome back, everyone. We'll now begin with the FDA presentation, beginning with Dr. Emily Freilich.

FDA Presentation – Emily Freilich

DR. FREILICH: Thank you, Dr. Montine.

My name is Emily Freilich. I'm the cross-disciplinary team leader from the Division of Neurology 1 for the new drug application for

AMX0035, for the treatment of ALS. I will present an overview of the available efficacy and safety data, which will be followed by a statistical presentation by Dr. Tristan Massie. I will then provide a few concluding remarks.

What does it mean for a drug to be effective? You have already heard from Dr. Buracchio that there are legal standards for the determination of efficacy, which require a drug to demonstrate substantial evidence of effectiveness. There are a few pathways that can be used to meet these standards.

A typical approach is the use of two adequate and well-controlled studies, which is a common way of independently substantiating that a drug has the effect that it is purported to have. Alternatively, there are situations -- especially when two studies may not be feasible, ethical, or practical -- when FDA may determine that it is sufficient to use a single adequate and well-controlled study plus confirmatory evidence. And finally, if a single study, typically a large

one, is exceptionally persuasive, it may sometimes serve to independently establish efficacy.

So what is the goal for today? As we have heard, there's a continued unmet need for new therapies for people living with ALS. That is not in question. We understand the importance of and need for new treatments to slow down the relentless progression of ALS and extend the life of people living with ALS. We also understand that ALS can be a heterogeneous disease, and that although most patients survive only 2 to 4 years from the onset of symptoms, 10 to 20 percent of patients may live longer than 10 years.

Our job today, and what we are asking for the committee's help with, is determining if the available data are adequate to conclude that AMX0035 is effective in the treatment of ALS. You will hear concerns that call into question the persuasiveness of the applicant's reported results.

This is a drug that does not have a highly targeted mechanism of action. Despite the reported results on the primary endpoint and on a post hoc,

open-label assessment of survival, there are methodologic and statistical concerns that make it challenging to conclude that the study results are not due to chance alone, especially given the underlying disease heterogeneity.

The question we have for you today is do the data from the single randomized-controlled trial and the open-label extension phase establish a conclusion that AMX0035 is effective in the treatment of patients with ALS? And if not, what additional data are needed to determine effectiveness?

As described by the applicant, AMX0035 is a fixed-dose combination of 3 grams of sodium phenylbutyrate and 1 gram of taurursodiol, commonly known as Turso or Tudca. ALS is a progressive neurodegenerative disease characterized by the death of motor neurons.

The applicant postulates that AMX0035 may reduce neuronal death by simultaneous inhibition of endoplasmic reticulum and mitochondrial stress. FDA notes that the pathophysiology of ALS is not

fully understood, but likely involves multiple complex processes and pathways. The purported mechanism is but one of a number of potential processes hypothesized to be involved in the pathophysiology of ALS.

I would like to give a brief summary of key regulatory interactions with the applicant. As you have heard, we held a pre-IND meeting in March 2016, at which point the division recommended the applicant use a combined analysis of survival and function, such as the joint rank, for the proposed CENTAUR study. This recommendation is routinely given to sponsors studying ALS and is included in the 2019 FDA guidance on drug development in ALS.

The IND was officially opened in April 2017. At a meeting on March 12, 2020, the division reviewed the top-line results of the CENTAUR study and questioned the robustness of the results and the ability of the study to serve as a single trial able to demonstrate substantial evidence of effectiveness. At that time, we recommended the

applicant begin work on a second efficacy study.

We met again in early 2021 and reiterated that although encouraging, more data would likely be necessary to support a marketing application. At that meeting, we discussed plans for a larger phase 3 pivotal study, which is currently ongoing.

Subsequent to that meeting, the division determined that the published survival benefit warranted a more thorough consideration of the data, and we invited the applicant to submit a request for a pre-NDA meeting, which was held in July 2021. The division encouraged the applicant to submit the NDA expeditiously to allow for earlier review of the data.

I will now give an overview of the CENTAUR study. CENTAUR was a randomized, double-blind, placebo-controlled study conducted at multiple sites in the United States. A total of 137 patients were randomized 2 to 1 to drug or placebo, with 89 patients receiving drug and 48 patients receiving placebo for 24 weeks. There were two patients who discontinued prior to any

post-baseline assessments and are not included in the primary analysis.

The study enrolled an appropriate ALS population for such a study. Patients were allowed to be on riluzole, which had to be stable for at least 30 days prior to enrollment. Once edaravone was approved in the U.S. in 2017, its use was also allowed.

During the study, 20 patients in the treatment arm discontinued, with 67 patients completing the study. Seven of those patients had also discontinued from the drug but completed all visits, leaving only 60 patients who were still on drug at the end of the study. Ten patients discontinued from the placebo arm, with 38 patients completing the study, one of whom had discontinued from the drug. Most of the discontinuations were due to patient decision, which included adverse events, disease progression, and withdrawal of consent.

We also note that there were additional deaths in the 24-week study that were not recorded

as a disposition event if the death was recorded after patient withdrawal, for a total of 5 deaths in the AMX0035 treatment arm and 2 deaths in the placebo arm.

This slide lists the clinical endpoints in the CENTAUR study. The primary endpoint was the rate of decline in the ALS Functioning Rating Scale-Revised and the ALSFRS-R at week 24. The ALSFRS-R measures 12 functional activities in 4 domains, including bulbar, breathing, fine motor, and gross motor domains.

Higher scores on the ALSFRS indicate better performance. The scale is administered by a clinician asking the patient to score their level of function for these various activities, and because of such, some items can be prone to subjectivity.

FDA agrees that the ALSFRS-R is an acceptable primary endpoint to measure functional change in ALS. Rate of decline is not generally the most appropriate approach to analyzing the treatment effect, as it assumes that the changes in

the ALSFRS is linear over time, which has not been established. Additionally, when deaths occur, a primary endpoint of function alone does not account for loss of data due to death during the study. This will be discussed further in the statistical presentation.

The key secondary endpoint was the rate of change in the Accurate Test of Limb Isometric strength, ATLIS, a measure of static muscle strength in each limb. The second secondary endpoint was the rate of change in plasma neurofilament heavy chain, a potential biomarker of neuronal degeneration and axonal injury. It may be hypothesized that a therapy that shows benefit in the treatment of ALS may also decrease pNF-H levels. Third in the hierarchy was a rate of change in slow vital capacity, or SVC, at week 24. SVC is a measure of respiratory function.

Survival, defined as the rate of death, tracheostomy, permanent assisted ventilation, and hospitalization at week 24 was last in the hierarchy of secondary endpoints. Inclusion of

tracheostomy and hospitalization in the definition of survival is problematic, as there may be considerable variability as to when to hospitalize a patient or perform a tracheostomy due to the differences in standard of care by the treating physician or patient preferences. Tracheostomy may also be placed in anticipation of the future need for ventilatory support.

In the forthcoming slides, I will introduce some of the efficacy results and potential concerns identified during the FDA review. Additional details will be provided in the statistical presentation as well.

There were no significant imbalances observed in the baseline demographic characteristics of the patients in the study. There were, however, a few imbalances noted in baseline disease characteristics. We note a better baseline ATLIS score in the AMX0035 group. This may indicate that these patients may have been stronger at baseline. On the other hand, baseline characteristics that appear better in the placebo

arm included a higher percentage of patients with limb-onset ALS and a higher percentage of patients on concomitant ALS medication at baseline, shown in blue.

FDA notes that in a small trial such as this, baseline imbalances are more likely to occur than in larger trials, and such imbalances are exaggerated by the 2 to 1 randomization. The number of imbalances indicates that the groups may be poorly matched. Baseline prognostic differences are possible and introduces uncertainty into the interpretation of the results.

It is also important to note a few issues during the conduct of the study. There was a randomization implementation error such that the first 18 patients -- 13 percent of the overall sample size -- were assigned to the drug arm because of a shipping error which resulted in the unavailability of placebo doses, and the subsequent 9 patients were then all assigned to placebo. The unblinded statistician was aware of this problem and attempted to adjust the pre-planned

randomization schedule to fix the problem. It is unclear the impact this may have had on the outcome of the study but we do note that it further contributed to the baseline imbalances, which will be further discussed in the statistical presentation.

Additionally, edaravone was approved after the study was initiated. Patients were allowed to start edaravone during this study. There was an imbalance in the number of patients in each arm initiating new treatment with edaravone during the study. A higher proportion of patients started edaravone after the baseline assessment in the AMX0035 arm compared to the placebo arm. This post-baseline starting of new concomitant ALS medication is a possible confounder for any noted treatment effect.

Finally, FDA also notes that the active drug contains a bitter taste and causes transient GI symptoms such as diarrhea and abdominal pain that are more frequently reported in the first 3 weeks after initiation. A bittering agent was added to

match the placebo in the double-blind treatment period, yet there were still a number of patients who were able to correctly guess which treatment they had received on exit interview.

The potential for diarrhea and bitter taste were described in the informed consent, which may have alerted the patients to these symptoms and could have led to functional unblinding during the study. These are potential review issues we have identified which contribute to the uncertainty of the results.

I will now give an overview of the applicant's efficacy analysis. The applicant reports a statistically significant mean treatment difference on the rate of decline in the ALSFRS of 2.32 points for AMX0035 compared to placebo. There were 7 deaths during the study, five on AMX0035 and two on placebo.

The primary analysis does not account for these deaths, which can confound the results of a functional analysis because of loss of data. In addition, there were also concerns regarding the

handling of missing data, which will be further discussed by Dr. Massie. On the prespecified analysis of rate of decline of ATLIS, the secondary endpoint, the applicant reports a non-significant difference of 2.8 compared to placebo in the total ATLIS score.

We note that the applicant also did exploratory analyses to look at the individual components of the ATLIS. However, here we note that the baseline imbalance in the total ATLIS score is completely driven by an imbalance in the upper ATLIS score, which was 3.3 points better in the AMX0035 group at baseline.

These differences in upper arm strength at baseline could have led to proportional slower decline in the AMX0035 group and may be the reason for the nominally significant p-value on the upper ATLIS component. We also note that these baseline imbalances could also be driving the changes noted in the ALSFRS.

Other secondary endpoints do not provide strong support for the primary result. There was

no significant differences between AMX0035 and placebo for the rate of decline of pNF-H from baseline, and pNF-H actually decreased more in the placebo arm. There was also a non-significant and numerically small treatment difference of 5 percent in the rate of decline in SVC compared to placebo, and we note that there was no survival benefit observed at 24 weeks, which is important to consider in the context of our later discussion regarding survival.

In summary, this is a small study with baseline imbalances noted between the treatment arms. As with any small trial, an impact of these imbalances on the outcome cannot be excluded. Additionally, there are issues that have been identified with the conduct of the study such as the randomization error further contributing to baseline differences, post-baseline imbalance in starting new medications, and the potential for functional unblinding.

Results of the primary endpoint are not highly persuasive and secondary endpoints are not

generally supportive of the primary endpoint. There is no survival benefit seen at 24 weeks. FDA does not believe that the most appropriate methods were used for the statistical analyses, which will be further discussed by Dr. Massie. In summary, the findings of the 24-week, double-blind CENTAUR study do not provide robust support for a treatment effect in patients with ALS.

I will now briefly review the open-label extension study and the results. Enrollment into the open-label extension was optional after the completion of the 24-week, double-blind phase. Ninety out of the original 137 patients enrolled in the open-label extension, with 34 percent of patients not participating in the OLE. A higher percentage of AMX0035-treated patients did not enroll in the extension study.

Most patients discontinued from the open-label extension with only 2 patients completing 132 weeks of treatment. This table includes the reason for discontinuation in the OLE. Please also note that only 55 out of 90 patients

who enrolled in the extension study remained at week 48 when the open-label efficacy analyses were performed.

The prespecified primary endpoint for the extension phase was safety with secondary objectives to assess efficacy at week 48. The applicant performed prespecified extended slope analyses for the ALSFRS, ATLIS, and SVC at week 48 and reported nominally significant positive results. These analyses compare patients originally randomized to AMX0035, RA, for those randomized to placebo, RP.

We note that these open-label efficacy results on the functional endpoints are difficult to interpret. Enrollment in the open-label extension was optional, with 34 percent non-participation and significant dropout during this study. As mentioned, only 40 percent of patients remained at the time of these week 48 analyses, which make it harder to interpret the extended slope because of the significant amount of missing data.

The protocol did not indicate that the blind to original treatment in the double-blind period was to be maintained or who among the patients, investigators, and site personnel were to remain blinded to the original treatment. Additionally, there was again potential for functional unblinding to treatment because patients may have experienced GI adverse events upon transition from placebo to active treatment.

It is noted that 44 percent of patients switching from placebo to drug discontinued due to adverse events in the OLE, and 75 percent of patients who had received placebo in the double-blind treatment period correctly identified that they had received placebo when asked during the exit interviews for the open-label phase. Additionally, there were 23 deaths by week 48, which are ignored in the slope analysis, and the same concerns regarding linearity of slope analyses applies here as well.

The applicant included a prespecified survival analysis in the open-label extension which

was a composite time-to-event analysis, including death, tracheostomy, permanent assisted ventilation, and hospitalization. The applicant reports a statistically significant increase in the composite survival time to event in the RA group compared to the RP group.

The composite time to survival endpoint was specified in the protocol, but when it would be performed was not prespecified. We note the survival analyses were done after multiple data cutoff dates, including September 25, 2019; February 29, 2020; July 20, 2020; and March 1, 2021.

An external firm was contracted to conduct a search for vital status based on the subjects' family notes, clinic notes, National Death Index, and Social Security Death Index, which did collect the vital status on most patients who had originally been in the trial, however, there are limitations to interpreting the composite survival analysis. As noted, there were a large number of dropouts in addition to the 34 percent

non-participation in the open-label phase. There is no information on the clinical care of patients after the study discontinuation.

There are limitations of including tracheostomy and hospitalization data in the composite survival endpoint due to the previously mentioned variability involved in the timing of tracheostomy placement and hospitalization. These were not systematically collected in the open-label phase. Additionally, there may be missing data after subjects terminated from the study, which would not be captured in the vital status sweep, including data on whether any of the alive patients were requiring permanent assisted ventilation.

Additionally, FDA notes that there were additional deaths that occurred after March 1st that are not counted in the reported analysis. Inclusion of these deaths changes the statistical analysis of survival and further illustrates the notion that in a small study such as this, a shift in a few deaths in either arm, in addition to the timing of the analysis, can make a big difference.

An additional post hoc survival analysis of time to death alone was performed. The applicant reports a nominally significant survival benefit on a supplemental time to death only analysis, showing a median difference of 4.8 months, and the details will be discussed in the statistical presentation. However, we also note limitations to this exploratory survival analysis.

This is a small study which had baseline disease imbalances in the treatment groups. The p-value is nominal and not highly persuasive. The timing of the analyses was not prespecified. The results appear to differ based on the cutoff date, and the apparent survival benefit that was initially noted in July 2020 had decreased in March 2021. We note that as of March 1st, 70 percent of patients randomized to drug had died compared to 73 percent of patients originally randomized to placebo.

We also found no apparent correlation between the duration of drug exposure and survival. There are many patients included in the survival

analysis who were randomized to drug but who dropped out of the study early or did not enroll in the open-label extension and are still contributing to the reported survival benefit. When looking at median survival in alive patients, patients on placebo who never received drug survived for a median 1,295 days, and patients who received AMX0035 for greater than 96 weeks in the study had a median survival of 1,237 days. Therefore, we need to ask ourselves if the noted survival benefit is by chance alone or due to underlying disease heterogeneity rather than an effect of the drug.

I will briefly give an overview of the AMX0035 safety profile. Overall, the 137 patients provided safety data in the combined controlled and open-label extension phase, with 43 patients receiving drug for greater than 1 year and 13 patients receiving AMX0035 for greater than 2 years. There were no significant safety concerns at the proposed dose. There were no differences in fatal or serious adverse events between drug and placebo, and most fatal or serious adverse events

were secondary to complications of ALS progression.

In the double-blind treatment period, patient discontinuations were higher in the treatment group compared to the placebo group, and common AEs mostly belonged to the GI system organ class, including diarrhea, abdominal pain, and nausea.

I will now turn to Dr. Massie for the statistical presentation.

FDA Presentation – Tristan Massie

DR. MASSIE: Thank you, Dr. Freilich.

I'll detail the statistical issues identified in the review of the application. FDA guidance indicates that a single trial to establish effectiveness should demonstrate a clinical and statistically very persuasive effect. Also, it should include both scrutiny of trial conduct including, for example, completeness of follow-up; methods of analysis; imputation of missing data; and evaluation of trial endpoints is critical.

There's uncertainty about the results from the single efficacy trial of AMX0035 and its

open-label extension, therefore, the division advised another phase 3 study was needed in March 2020 and February 2021 meetings in order for the efficacy of AMX0035 to be established.

The AMX3500 study was a multicenter, randomized, double-blind, placebo-controlled superiority study with an open-label extension in adult patients with ALS. The study included two treatment groups: AMX0035 combination product; placebo; 2 to 1 randomization ratio, drug to placebo. Key efficacy outcomes were collected at weeks 3, 6, 9, 12, 15, 18, 21, and 24. The primary endpoint was the ALSFRS-R at week 24.

The issues with this application are, first, the single study with evidence in the primary analysis that is not persuasive, a p-value of 0.034 and a corresponding week 24 difference of 2.32 points on a 48-point ALSFRS-R scale. Second, there are issues with study conduct and analysis assumptions.

Many sensitivity analyses provide less persuasive results than the primary analysis. In

particular, there were issues with randomization implementation and imbalance in use of concomitant ALS medications riluzole and edaravone. Additionally, there are issues with the handling of deaths or lack thereof and missing data assumptions in the primary analysis.

Also, the primary analysis assumption of linearity over time and treatment effect is questionable based on the observed data and the prespecified analysis plan. Furthermore, secondary endpoint results are not strongly compelling. Finally, with regards to the open-label extension, survival analyses for time to death alone are exploratory and not persuasive.

There are two key analysis populations for this study: first, the intent-to-treat, or ITT, population, defined as all randomized patients who received at least one dose of study drug; and second, the modified intent-to-treat population, the mITT, defined as all randomized patients who received at least one dose of study drug and had at least one post-baseline ALSFRS-R assessment.

Primary analysis was a mixed effects model with ALSFRS-R linearity slope assumption in the mITT population. Model fixed effects included an intercept, week corresponding to the slope assumption; interactions between the retrospective pre-randomization slope week; as well as between patient age and week; and finally between treatment group and with slope.

The model also included random effects -- that is random adjustments to the group intercepts and slopes -- for individual patients. This model assumes missing ALSFRS-R data is missing at random, including for deaths before week 24 and after deaths for these patients.

Here's the timeline of key events for the AMX3500 study. March 6, 2019, FDA finalized comments on the statistical analysis plan for AMX3500 to present to the applicant. On October 15, 2019, a revised final analysis plan was submitted by the applicant. November 5th, a final separate analysis plan for the open-label extension was submitted by the applicant.

The applicant reported that November 26, 2019 was the date of unblinding of the double-blind period data. December 16, 2019, the applicant made a press release citing positive double-blind results. March 12, 2020, there was a Type C meeting between the applicant and FDA. In addition to reporting top-line results for the double-blind period at this meeting, the applicant also reported an analysis of the survival composite endpoint, as well as time to death or death equivalent of the open-label extension data, including death or death-equivalent events through September 2019.

April 1, 2020, the applicant submitted a supplemental open-label extension analysis plan for survival specifically. Finally, March 1, 2021 is the death event cutoff and the applicant's final survival status sweep informing the final open-label extension survival analysis.

Notable FDA comments sent to the applicant regarding the statistical analysis plan for AMX3500 included the need to specify the estimand for the primary analysis, including how to handle

intercurrent events such as death. This included a recommendation for a joint rank analysis of function and survival being the primary analysis. The importance of backup sensitivity analyses for missing data and linearity assumptions was also conveyed.

The applicant provided responses to these comments on August 26, 2019, including lack of agreement with the joint rank analysis being primary, and the applicant later submitted a revised analysis plan, which was received by FDA on October 15, 2019.

There was a randomization implementation issue in the AMX3500 study, particularly the first 18 patients in a row all received drug due to a shipping problem resulting in unavailability of placebo doses [indiscernible]. The unblinded data monitoring committee statistician noticed this at the first meeting of the study DMC and made changes to adjust the randomization, including the next 9 patients in a row all receiving placebo.

The applicant has reported as-treated

results for those affected by this shipping issue, not as randomized results. This weakens the integrity of the results slightly as the validity of the analysis rests on using the as-randomized intent-to-treat assignments. The applicant's sensitivity analyses, including the patients affected by this randomization shipping issue, have slightly less favorable p-values, with the open-label, time to death analysis losing nominal significance.

This slide details the treatment group imbalances in use of concomitant ALS medications edaravone and riluzole observed for the study. With baseline, there was a higher proportion of the placebo group edaravone, 50 percent versus 25 percent for drug, as well as a higher proportion of the placebo group using riluzole, 77 percent placebo versus 68 percent for drug.

On the other hand, post-baseline initiation of the ALS medications riluzole and edaravone was higher in the drug group, 16 percent for drug versus 4 percent placebo, and there was no

imbalance at baseline in ALSFRS-R. This excess of ALS treatment intercurrent events in the drug arm may affect the interpretation of the study results; that is whether the treatment group difference is only due to the experimental treatment.

The applicant's primary analysis did not account for deaths in the first 24 weeks and occurred at a 5.6 percent rate for the drug group and 4.2 percent for placebo. This creates a potential for corresponding bias in the primary analysis, assumes missing at random after death, and doesn't include 2 deaths with no post-baseline ALSFRS-R.

It is more appropriate to combine survival and function considering death as an unfavorable outcome such as with the joint rank analysis. The mITT population used for the applicant's primary analysis excluded all patients without post-baseline ALSFRS-R assessments, thus excluding 2 deaths on drug occurring prior to post-baseline FRS-R assessment. Therefore, sensitivity analyses in the ITT population are particularly important.

There was considerable missing ALSFRS-R data at week 24 in this study, 17.4 percent for placebo and 17.9 percent for drug, among those who survived to week 24. The applicant's primary analysis relied on a missing-at-random assumption for this missing data. The applicant's sensitivity joint rank analysis for which no details were prespecified in the analysis plan relied on the last observation carried forward method for handling missing data in survivors.

This LOCF method relies on an unrealistic assumption of no worsening after dropout, and is especially unrealistic in a progressive disease like ALS. LOCF also does not appropriately capture statistical uncertainty in missing values.

The FDA reviewer used a missing-at-random-based multiple imputation approach in the reviewer's implementation of the joint rank analysis. Multiple imputation captures some of the uncertainty in missing values. This analysis still involves a strong and unverifiable missing-at-random assumption.

As shown here in the table of the joint ranked analysis results, the FDA analysis incorporating deaths by a joint rank test provides less persuasive evidence. The FDA analysis included the two ITT deaths not included in the mITT population and used multiple imputation under a missing-at-random assumption for missing data rather than the last observation carried forward, which is only valid under a more restrictive missing completely at random assumption the sponsor had used.

The applicant's implementation of the joint rank also ranked the covariates of age and pre-randomization slope in the analysis of the covariance of the joint ranks used to determine the joint rank p-value. Its ranking of covariates was not prespecified, as no details of the sponsor's joint rank imputation were, and the FDA reviewer noted that analyses without ranking these covariates tended to produce slightly higher p-values. But for consistency, the FDA reviewer's reported analysis in the table also ranked

covariates and that the applicant's alternative prespecified sensitivity analysis for death -- the so-called left-censored analysis -- is not shown here because it is problematic and thus inconclusive, as was detailed in the FDA comments in the briefing package.

This slide shows the quadratic and mean-per-visit repeated measures models suggest potential non-linearity of ALSFRS-R over time and optimistic bias at week 24 for the primary slope model. Slope model overshoots the placebo means in the beginning and middle of follow-up and undershoots the placebo mean at week 24. Visual plots used for model diagnostics, not shown here, also suggested potential non-linearity of the ALSFRS-R an inferior model fit for the slope model.

The table in this slide suggests a sensitivity to the linearity assumption underlying the applicant's primary analysis. It shows that sensitivity analyses allowing for non-linearity provide less persuasive evidence. IND stage comments provided to the sponsor on the analysis

plan -- the FDA had indicated that linearity should be assessed in a prespecified objective way -- should be a backup analysis for non-linearity but that slope models ignoring of deaths can cause bias, and so the joint ranks should be primary if there were deaths.

The sponsor presented results for a different quadratic model in the study report and AC briefing package shown in the first row in this table has a more favorable result than the prespecified quadratic model shown in the second row, but the former is a post hoc model, so unreliable. There's a fairly big difference in the p-values of the post hoc and prespecified quadratic models, p equals .0385 for the post hoc model and 0.1134 for the prespecified one.

Neither of these quadratic models allowed the quadratic term to vary by treatment group, which may be unrealistic in the setting of a quadratic model. Therefore, the FDA reviewer extended the prespecified model and allowed the quadratic term to vary by treatment group. The

result is shown in the third row with the p-value of 0.0644.

None of these quadratic models is ideal, in general, for non-linearity situations, which is why the FDA neurology statistical team usually recommends a mean-per-visit repeated measures model in order to get an unbiased estimate of the treatment difference at the last visit while avoiding a questionable linearity assumption. That is when deaths are not expected in the study.

The results of this non-linear compatible model is shown in row 4 to have an estimated week 24 treatment difference of 1.86 with a p-value of .0749, but again, this model also ignores deaths.

The secondary endpoint results in Study AMX3500 are not persuasive. The first key secondary, ATLIS, a measure of strength, has three possible summaries of interest, and the analysis plan was not clear on which was primary. Only the upper ATLIS component is nominally significant with a p-value of 0.042. The total, which would be the

most likely primary summary, is not nominally significant.

The ATLIS analyses also ignored deaths and have slightly more missing data at week 24 with the ALSFRS-R. The rest of the key secondary endpoints shown in the prespecified order of priority were not nominally significant. These include slow vital capacity; neurofilament biomarker pNF-H positive survival endpoint; time to first event of hospitalization, tracheostomy, or death.

Turning to the up to 132-week open-label extension study, the primary objective was to evaluate general safety. Here, it's protocol specified efficacy endpoints; ALSFRS-R rate of decline; positive survival endpoint of time to first hospitalization, tracheostomy, or death; upper and lower ATLIS scores rates of decline; rate of progression on the ALSFRS-R subdomains; rate of progression on total ATLIS score.

Time to death alone was not specifically included in the list of efficacy outcomes or objectives. Analysis of time to death alone was

included in the description of analyses of the components of the composite survival endpoint and was not given priority relative to the other two components, hospitalization or tracheostomy, or relative to the composite itself. Prespecified composite survival endpoint analysis was to be based on a Cox proportional hazards regression with age and pre-randomization slope as covariates.

The primary objective of the open-label extension of the AMX3500 study was safety, followed by the objective of investigating progression on the ALSFRS-R -- time to the composite, event of hospitalization, tracheostomy, or death; progression on the ATLIS function measure; and progression on slow vital capacity.

The results for all endpoints except death are very difficult to interpret due to substantial dropout and missing data and many deaths. In particular, only 66 percent of patients entered the open-label extension. Only 40 percent have week 48 ALSFRS-R measurements, and there's 15 to 20 percent mortality by week 48, which is ignored in the

applicant's extended slope analysis. Linearity assumption for these endpoints over time are for a longer period, yet another limitation given the questionable linearity in the shorter period.

Supplemental open-label extension statistical analysis plan for survival was drafted after the sponsor had already analyzed survival data from the open-label extension after the last patient last visit in the double-blind period. This supplemental analysis plan shifted the focus from the survival composite of hospitalization, tracheostomy, or deaths that were listed as an objective in the open-label extension protocol, the endpoint of time to death alone, which had not been specifically listed as an objective in the protocol. The supplemental analysis plan specified a Cox proportional hazards regression time to death alone with age, baseline ALSFRS-R, and pre-randomization slope as covariates.

The figure here shows Kaplan-Meier estimates of overall survival based on time to death only through the open-label extension. Note that there

was no re-randomization for the open-label extension. A moderate proportion of 35 percent did not participate but that vital status as of March 1, 2021 was obtained for purportedly all but one randomized patient. It's important to note that the original placebo group continues into the open-label extension, switched to AMX0035 treatment.

Using the supplemental analysis plan methods, the covariate adjusted hazard ratio for time to death between the two groups was estimated as 0.64, the 95 percent confidence interval ranging from 0.42 to 1.00, based on the final vital status searches death event cutoff of March 1, 2021.

DR. MONTINE: Excuse me, Dr. Massie. This is Tom Montine. It's time for you to wrap up, please.

DR. MASSIE: Okay. Well, I think I can just turn it back over to Dr. Freilich in that case.

FDA Presentation – Emily Freilich

DR. FREILICH: Thank you, Dr. Massie.

I will now focus on the final focus of our

discussion this morning. We want to acknowledge that there is a pivotal phase 3 study currently underway, which is a 48-week, double-blind, placebo-controlled study in 600 patients. The study should complete in late 2023. The primary endpoint is a joint analysis of survival and function as measured by the ALSFRS-R.

We need to consider how this study will fit with the available existing evidence. A positive study could combine with the CENTAUR results to convincingly support the benefit of the drug in the treatment of ALS, but what would it tell us about the efficacy of the drug if that study is negative?

Finally, I want to leave you with our question for the committee today. There will be a single voting question.

Do the data for 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 ALS?

There will be a discussion of the vote, and

if you vote no, we would ask you to please discuss what additional information you would consider necessary to establish a conclusion that sodium phenylbutyrate and taurursodiol is effective in the treatment of patients with ALS. Thank you.

Clarifying Questions to the FDA

DR. MONTINE: Thank you, Dr. Freilich. Thank you, Dr. Massie.

We will now move to the clarifying questions for the FDA. The format will be as before. Please raise your hand. I will acknowledge you. When acknowledged, state your name for the record. Direct your question to Dr. Freilich or Dr. Massie if you can, or to a specific slide if you can. Please signal when you're done, and then push the icon again to lower your hand.

We have lots of hands up, so in the interest of time I would ask that you please limit yourself to your two most pressing questions, and then we'll cycle around as time permits. If we have time remaining at the end of this session, we'll return to the remaining questions for the applicant, and

if we don't have time, we will later after the open public hearing session for additional questions.

So again, I'm just going to do this in the order in which I see the list, if that's ok.

Dr. Nath, you're at the top of the list.

DR. NATH: Thank you very much. Avi Nath here. First of all, I want to thank the FDA for such as very thorough analysis that they've done and of the study. It was very helpful.

I have one single question, and that is, since most of the efficacy rests on the Functional Rating Scale and there's a subjective component to it, the issue about blinding or unblinding is really critical to understanding the effect of the treatment, so there's a discrepancy.

The investigators were very comfortable that the patients were not unblinded, however, the FDA thinks that the side effects were such that the patients were unblinded. So if somebody could clarify for me as to whether the patients were unblinded or not, it would be very, very helpful. I mean, how do we reconcile these things?

DR. FREILICH: This is Dr. Freilich. Thank you, Dr. Nath, for that question.

I would clarify that we do not know with any certainty that patients were unblinded. We had merely raised it as a review issue that there was a potential for unblinding as we analyze in any clinical trial when there are distinct adverse events such as the diarrhea and abdominal pain; that that could be a contributor to patients knowing which drug they were on and potentially leading to uncertainty in the interpretation of the results. We obviously can't know with any certainty if the patients were unblinded or not. We were just raising that as one of our concerns.

DR. NATH: Thank you. That's very helpful. Over.

DR. MONTINE: Thank you.

Dr. Traynor, please.

DR. TRAYNOR: Hello. This is Bryan Traynor. Actually, I think my hand was raised from the applicant session, so my question is more appropriately addressed to the applicant when we

get an opportunity.

DR. MONTINE: Great. Thank you. I'll be sure to come back to you.

Dr. Follmann, you have the floor.

DR. FOLLMANN: Yes. Thanks. This is Dean Follmann. I have two questions, and I think the first one is for Dr. Massie on page 36, slide 36. You did an ITT analysis, I guess, of the joint rank model, and I was wondering if you also did an mITT analysis of the joint rank model.

DR. MASSIE: Yes. I also did an mITT analysis. I think the p-value for that was 0.5.

DR. FOLLMANN: Alright.

One thing I'm sort of puzzling about is the strength of evidence of the survival difference between the two arms. And one thing, thinking through, is this really doesn't show up until after the placebo crossover, so everyone is on drug, and I wondered if you or Dr. Freilich had thought about that aspect of the survival benefit. It shows up during a period where both are on drug.

DR. FREILICH: Thank you, Dr. Follmann.

This is Dr. Freilich. I can start and see if Dr. Massie wants to add anything.

We had that consideration as well, and we do not have an explanation for why the survival benefit appeared later. I think one of the other things to note is that so many of the patients had discontinued; that even though the applicant was able to collect data, vital status data, on so many patients that had originally been in this study on March 1, 2021 to do the survival analysis, the duration of time on drug is very variable, and we noted that some patients really only received a few weeks of drug, total or a few months at the most. So it is one of the things that we are uncertain about as well.

DR. FOLLMANN: I see. So there was some discontinuations of drug on patients who were receiving drug regardless of what they're randomized to, and they're still counted in the survival analysis, obviously.

DR. FREILICH: Exactly.

DR. FOLLMANN: I was sort of thinking

everyone was on drug more, but that's not at all correct. Okay. Thanks.

DR. FREILICH: Exactly.

DR. MONTINE: Great.

DR. FOLLMANN: Thank you. Over.

DR. MONTINE: Thank you.

Dr. Caleb Alexander?

DR. C. ALEXANDER: Yes. This is Caleb Alexander. For Dr. Massie, a question about the non-linearity assumption.

Do you agree with the sponsor that the non-linearity assumption was not violated? And if so, then is the shared baseline model problematic, setting aside the issue of deaths? Which I'll come to in a second?

DR. MASSIE: This is Tristan Massie. I believe that there's a gray area. It's very close to violation. A condition was that there had to be quadratic terms, couldn't have a p-value less than 0.10.

DR. C. ALEXANDER: Okay.

DR. MASSIE: And one of the four has a

p-value of 0.1016, so that's one-thousandth of a point. There are other ways to look at model fit like likelihood ratio tests and key information criterion. Those common measures seem to suggest that the quadratic model is actually a better fit. So it depends on what the prespecified plan was, but maybe that was not quite optimal. But I think there is definitely a gray area, and we're not convinced that linearity is appropriate.

DR. C. ALEXANDER: Okay. And the issue of death, in the materials, there are varied reflections on whether the shared baseline model is problematic. It's problematic if there are lots of deaths, but maybe not if there are a few. So there were 7, I think, out of 137, or about a 5 percent mortality rate if I understand, or 5 percent of the subjects, the deceased within the first 24 weeks.

Can you just comment, is that a lot, a little, clearly too many to manage with a shared baseline model or not, as long as there are sensitivity analyses performed?

DR. MASSIE: It's not a lot, but there is

slightly a higher proportion in the drug group, which is concerning. And in addition, the model assumes that after death, any missing data after death, it assumes it's missing at random, which is a problem and likely introduces bias. So I think with slightly more deaths in the drug group, we're very concerned with the model and ignoring deaths.

DR. C. ALEXANDER: Thank you. That's the end of my questions.

DR. MONTINE: Thank you.

Mr. Weston, please?

MR. WESTON: I also had a question.

Thank you, Mr. Chair. I have a two-part question if there's time for a full answer. My question is for either Dr. Freilich or Dr. Massie, whoever's best suited to respond.

Five years ago, the FDA's May 5, 2017 news release announcing the approval of Radicava stated, in part, that every 24 individuals receiving edaravone, or Radicava, declined less on a clinical assessment of daily functioning compared to those receiving the placebo.

My question is, can you please compare the changes from baseline to week 24 in ALSFRS scores for both today's drug, AMX0035, as well as Radicava? And if you don't have this at hand, the reference to Radicava data is contained in the study of Japanese persons with ALS in summarized pages 7 through 9 of the FDA's approval package from 2017.

I'll hold off on my second question just in case we run out of time.

DR. MONTINE: Thank you.

DR. FREILICH: Thank you, Mr. Weston, for that question. I'm going to turn to Dr. Buracchio, who can answer this comparison to edaravone.

DR. BURACCHIO: Hi. This is Teresa Buracchio. On a superficial look, the results in the edaravone study do look comparable to the Amylyx study, but there are marked differences actually between the studies.

In the edaravone study, they had, I believe, no deaths in this study, and Dr. Massie may be able to comment on this further. But I believe they did

use a change from baseline analysis there that was not a joint rank analysis, and that was acceptable because they did not have any deaths. The actual treatment difference was around 2 and a half points, which is what is similar to what was being reported in the Amylyx AMX0035 analysis.

The other difference is that the results in the edaravone study were very robust. There were persuasive results on the initial analysis with small p-values on the primary endpoint, and then also secondary endpoints were supportive and also had small p-values.

So in that situation, the edaravone approval was a single study with a similar reported change on the ALSFRS, but the study results overall were just much more robust than what we are seeing in the AMX0035 data set, where we have a single result on the primary endpoint that is a p-value of .03. It's not really supported by the primary endpoint, and we have questions about the appropriateness of the analysis because of the occurrence of deaths.

Dr. Massie, is there anything more you would like to add to that?

DR. MASSIE: No, I don't really have anything to add. I think you covered it.

DR. FREILICH: Thank you.

MR. WESTON: Yes, thank you. That answered my second question as well, so I'm done.

DR. MONTINE: Thank you, Mr. Weston.

Dr. Fischbeck?

DR. FISCHBECK: Yes. I have a couple of questions I guess mostly for Dr. Massie, but maybe Dr. Freilich.

Just in terms of the impact, it seems like it's best referring to the study as partially randomized because the first 27 participants were not randomized appropriately, and I wonder about the impact of that. Is that really a problem, or not, in terms of statistics? That's the first question.

DR. MASSIE: This is Tristan Massie. I think it's definitely an issue, the strength of the study. Really, the gold standard is randomization

because it balances all other potential confounding influences on the outcome, and compromising of the randomization could undermine the validity of the statistical inference.

The sponsor did look at excluding the first 27 patients affected by the shipping issue, but that creates a different size study, and it's just less than ideal to have an issue like this with a small study in a single study setting.

DR. FISCHBECK: Thanks. My other question was about revising the SAP after unblinding. It seems to me that that's, well, not acceptable, and you'd like to have the statistical analysis plan B prospective; and is it a real problem to revise the analysis plan after the data has been unblinded?

DR. MASSIE: Yes, that would be a real problem. I think it was done because of what they had seen when they first looked at the survival data. I think they claimed that the author of the revised SAP hadn't had any access to the data, and there was actually only one minor change to the analysis plan, and it was adding an additional

covariate based on ALSFR in the Cox regression. But I think the real issue is elevating time to death alone endpoint because, really, it wasn't listed in the objectives or the endpoints for the open-label extension before [inaudible].

DR. FISCHBECK: Thanks.

DR. MONTINE: Thank you.

Next on our list is Dr. Robert Alexander.

DR. R. ALEXANDER: Thanks, Dr. Montine. This is Robert Alexander. I have a question for Dr. Freilich related to slide 11 when you're talking about potential differences between the treatment groups.

You noted that there was a higher proportion of patients in the placebo group that were on standard of care at study entry, and that was something possibly in favor of placebo. But isn't it an alternative explanation that that reflects that they were actually more advanced or had more severe illness, and that's why their doctors had initiated that treatment prior to the study start?

Comment on that. Thanks.

DR. FREILICH: Thank you, Dr. Alexander, for that question. This is Dr. Freilich.

Yes, I would agree with you that that was one of our concerns as well, that the reason for the imbalance could have been the reverse; that patients on placebo may have been worse or be more aggressively treated. It seems like the imbalances could influence the study in any number of ways. We wanted to point out, though, the fact that there were more patients in the placebo arm on concomitant medications as kind of a fact that also may have led to differentiation in the progression of the disease.

DR. MONTINE: Thank you.

Dr. Follmann?

DR. FOLLMANN: Yes. This is a question for Dr. Freilich I guess partly related to your emphasis on the bar, I guess, for a single study, and you want the evidence to be quite persuasive and so on.

The sponsor talked about, I would say, that the CENTAUR study was relatively a more homogeneous

inclusion criteria relative to PHOENIX, which was more heterogeneous. And I wonder if you had thoughts about if, in fact, that's true, that CENTAUR had more restrictive inclusion criteria and how this single study might be applied more generally to people in the U.S. with ALS. Over.

DR. FREILICH: Thank you for that question. I don't know if we can speak to how homogeneous the population was in total. Like we said, we do notice imbalances in the population, and there likely are others that are not measured. However, their point is correct that the inclusion criteria were a little more restrictive in the CENTAUR study, where the patients had to have certain criteria in terms of the rate of decline at the time of initiation of the study, which was their attempt to capture a population in which you might be more likely to see a treatment benefit.

In terms of the applicability to the U.S. population, I think it's hard to know because --

DR. FOLLMANN: Okay. Thank you.

DR. FREILICH: -- of the unseen differences.

DR. FOLLMANN: Right. Thank you.

DR. MONTINE: Thank you.

Dr. Caleb Alexander, please?

DR. C. ALEXANDER: Yes. Caleb Alexander, and just a small point about eligibility or enrollment in the open-label extension.

I thought in the briefing materials we were provided, the sponsor said that 92 percent of eligible patients that completed randomization were enrolled, whereas the FDA, I believe you're reporting that 66 percent enrolled. There are a number of other questions and, I think, concerns that have been raised. But if I understood correctly, I was just curious what accounted for that discrepancy.

DR. FREILICH: Sure, Dr. Alexander. Thank you for that question. I believe the discrepancy is that we were mentioning that 66 percent of the total population did not enroll. So from the initial 189 patients, there was only 34 percent -- only 66 percent continued into the study; 34 percent did not.

The applicant was mentioning that of the patients who completed the study on drug, which would be the eligible patients to continue into the open label, 92 percent of those did continue.

DR. C. ALEXANDER: Oh, I see. Okay. Thank you. That's very helpful.

Then a question about plasma neurofilament heavy chain; can you speak a little bit, or someone on the FDA team, about the totality of evidence supporting its utility as a valid biomarker in this disease?

DR. FREILICH: Sure.

Dr. Buracchio or Dr. Dunn, would you like to talk about the biomarker data for NF, neurofilament heavy chain?

DR. BURACCHIO: Hi. This is Teresa Buracchio. We've seen neurofilament assessed as a biomarker in a number of neurodegenerative diseases. It is thought to be a marker of neuronal injury or axonal injury, and it appears to be elevated in patients with neurodegenerative processes.

As I mentioned, it's being studied in many different neurologic diseases, particularly the neurodegenerative diseases. I think that there are some data that show in a variety of different diseases that levels are elevated and may track with the disease course. It is being examined as a biomarker in a number of studies. It is not yet at a point where we would -- we still consider it exploratory, but we do see it as a promising biomarker.

So it is being included in a lot of studies, with the idea that if there is a reduction in neurofilament levels, that that would be suggestive of an effect on the slowing or reducing the degeneration being seen in the disease.

I think, as I mentioned, we're at the point now where we see this as a promising biomarker, but we still see it as an exploratory biomarker, and we're hoping to continue to collect more data on it to see how useful it will be in clinical trials going forward.

DR. C. ALEXANDER: Thank you. That's really

helpful. So out of curiosity, in the trials of the other two products that have been FDA approved for the treatment of ALS, was plasma neurofilament heavy chain assessed, and if so, did it track with disease progression or with drug exposure in the expected directions?

DR. BURACCHIO: it's a relatively new biomarker, I think maybe in the last five or maybe 10 years; I'm not exactly sure how long. We've been seeing it more and more over the last three or four years, I would say.

DR. C. ALEXANDER: Yes.

DR. BURACCHIO: The riluzole program, which was approved in the '90s, would not have had that. I think even the edaravone program, I believe that edaravone was approved around 2016, I think, and even that may have been a bit early for the inclusion of neurofilament in those studies. So, unfortunately, we don't have any information on how that performs in those studies.

Billy, do you want to comment? Dr. Dunn?

DR. DUNN: Sure. I'm happy to. This is

Billy Dunn.

Thank you, Dr. Alexander for that important question. We think it is a very important question to ask. The way you phrased your question raises a lot of issues using things like validated biomarker and the breadth of its use.

I think something very important to keep in mind here -- I certainly concur with what Dr. Buracchio said -- is neurofilament light we feel is an important aspect of the development program targeted at mitigating neurodegeneration. It is a marker of neurodegeneration or neuronal injury, and should we have seen an effect on neurofilament, we would have paid attention to that. We asked about it directly, several times, during development with the sponsor.

It is a measure that while not suitable for use as a stand-alone measure, one could certainly envision a situation where an effect in what ostensibly is a beneficial direction here would have provided important contextual and supportive information of, again, an ostensibly beneficial

effect on the clinical measure.

Similarly, the lack of an effect here on that measure is something which we found to be part of the overall character of data that we see that does not provide robust support for the primary measurement, so we think it's appropriate to capture here.

Quite honestly, in the interest of having an effective medication available to ALS patients, I think all of us in this space would have preferred to have seen a directional benefit there that was convincing. We didn't, and we think that is of some concern in the overall picture that shouldn't be construed as elevating the use of neurofilament to some kind of independent measure that's suitable on its own for assessment. But we do think it's a very important part of the contextual picture, and we do see it used fairly broadly in these types of diseases.

I hope that answer helps flesh out what you've already heard.

DR. C. ALEXANDER: Yes, it does. Thank you

very much.

DR. MONTINE: Thank you.

Dr. Jones, I saw your hand was up, but it's now down. Did you have a question you'd like to ask?

(No response.)

DR. MONTINE: Well, we've reached time, and we can follow up with Dr. Jones --

DR. JONES: Oh, I'm sorry. I was on mute. I am so sorry.

DR. MONTINE: No problem at all.

DR. JONES: Can I do my question? Is that ok?

DR. MONTINE: Please do.

DR. JONES: Okay. My question was related to, I believe Dr. Massie stated that one of his major concerns was about the elevation of the time of death, using as an endpoint or measure.

My question is, if a study does show something as significant as a change of time in death, what would the FDA have liked to have seen by the applicant if one of these findings is

something that was not indicated in the original intent of the study? Thank you.

DR. MASSIE: This is Tristan Massie. I think given that it was not in the objectives or endpoints for the open-label extension, specifically as time to death alone -- a survival difference can occur due to chance alone at a rate of 1 in 20 trials -- you have to be careful about it wasn't listed in the endpoints. We consider the low prior expectation of a survival benefit here. When we are left with a borderline p-value, it doesn't add up to a take-away belief, a strong take-away belief of a true survival difference.

DR. MONTINE: Thank you.

DR. FREILICH: This is Dr. Freilich. I just wanted to add -- sorry, Dr. Montine.

Let me just add to that, that I think that was a good question, Dr. Jones. I think if we saw a benefit on death, we obviously consider that very important, as you mentioned, so we definitely would look at it, and analyze it, and consider it meaningful even if it wasn't prespecified.

However, the concerns here are with the persuasiveness of the results and the fact that it was not expected and not prespecified, work against it to decrease the persuasiveness when we already had some concerns about the interpretation of the survival benefit.

DR. MONTINE: Thank you, Dr. Freilich.

Thanks to the panel members, Dr. Freilich, Dr. Massie. Thank you, all, for a great discussion. It's now time to break for lunch. We'll reconvene at 1:55 Eastern time, so that's just under 45 minutes from now.

Two comments for the panel members; please return about five minutes early so we can be sure everyone is online and ready to go at 1:55. Also, panel members, please remember that there should be no discussion of the meeting topics with other panel members during the break.

Okay. We'll reconvene at 1:55. Thank you.

(Whereupon, at 1:14 p.m., a lunch recess was taken.)

A F T E R N O O N S E S S I O N

(1:58 p.m.)

Open Public Hearing

DR. MONTINE: Welcome back. I'm the chair of the Peripheral Central Nervous System Drug Advisory Committee meeting, and we will now begin the open public hearing session. I have a few comments before we begin

Both the FDA and the public believe in a transparent process for information gathering and decision making. To ensure such transparency at the open public hearing session of the advisory committee meeting, FDA believes that it is important to understand the context of an individual's presentation.

For this reason, FDA encourages you, the open public hearing speaker, at the beginning of your written or oral statement to advise the committee of any financial relationship that you may have with the sponsor, its product, and if known, its direct competitors. For example, this financial information may include the sponsor's

payment of your travel, lodging, or other expenses in connection with your participation in the meeting.

Likewise, FDA encourages you, at the beginning of your statement, to advise the committee if you do not have any such financial relationships. If you choose not to address this issue of financial relationships at the beginning of your statement, it will not preclude you from speaking.

The FDA and this committee place great importance in the open public hearing process. The insights and comments provided can help the agency and this committee in their consideration of the issues before them.

That said, in many instances and for many topics, there will be a variety of opinions. One of our goals for today is that this open public hearing be conducted in a fair and open manner, where every participant is listened to carefully and treated with dignity, respect, and courtesy. Therefore, please only speak when recognized by the

chair. Thank you very much.

We have 26 speakers. You'll see the clock up in the corner that will count down the time that's allotted to you. Please do your best to keep to time, and I will gently remind you if you're exceeding the time allotted.

With that, speaker number 1, your audio is now connected. Will speaker number 1 begin and introduce yourself? Please state your name and any organization you are representing for the record.

MR. DERBY: Thank you. My name is Jeff Derby. I live in White Rock, British Columbia Canada. I am not receiving any payment from Amylyx for my presentation today.

I feel the reason I can even talk to you today is a result of having accessed AMX0035. My journey is similar to many ALS patients. In 2017, I had weakness in my hand during a fishing trip but did not take it too seriously. Several months later, I noticed weakness again, and then we started the process of visiting our family doctor, three different [indiscernible], three

neurologists, before I was diagnosed with ALS July 2018.

Looking back, we could see from videos that I had nerve twitching in my arm during the summer of 2016 [indiscernible]. The message the neurologists gave me and my family was plan your affairs, travel all you can, eat whatever you want because the timeline for survival is 2 to 5 years.

The only treatment available to me in 2018 was riluzole, which would slow down ALS by a few months. At that time, edaravone was not approved or available except through the special access program. I applied and was approved for the SAP to receive edaravone. This is not an easy treatment as it requires a port, a home nurse, and 10 days a month of infusions. I have been receiving edaravone since December 2018.

My family became my research team, as our neurologists had no information about the trials. They found the AMX0035 trial out of the Swedish Medical Center in Seattle, Washington. I was accepted and began the trial in September 2018.

After the trial period ended March 2019, I was given the opportunity to go on open label and now currently receive the drug on a compassionate care program.

I started, as I said, with weakness in my right hand and arm, and it has moved to my left hand and arm, as well as my legs are feeling weaker. The difference from many, although I'm weaker now, I can still use my arms, legs, as well as talk, breathe, and continue to drive. I'm still independent. This is after almost four years from diagnosis, six years from onset.

I believe every ALS patient should have the opportunity to have AMX0035 because I've seen real benefits. It is not a cure, but in my real-life results, I have seen six ALS patients in my social circle over the past two years pass away without it, and yet their timeline was similar to mine, and most were receiving riluzole and edaravone treatments. I have been taking probiotics to help with any GI side effects and have found warm to hot water helps with the taste. Compared to edaravone,

AMX0035 is very easy to take.

I ask today that you consider this decision as if you have a personal connection to somebody with ALS, a parent, brother or sister, a son or daughter, or a friend. AMX0035 trial results showed an improvement, extending life for many. Even if it is only 6 and a half months, would you not want that for them?

For the ALS patient, I do see a better future. There are so many trials in the [indiscernible], but today we need AMX0035 for all ALS patients so they can be alive for the future. Thank you for your time.

DR. MONTINE: Thank you. Thank you very much.

Speaker 2, your audio is now connected. Will speaker 2 begin and introduce yourself? Please state your name and any organization you are representing for the record.

MR. BURGHARD: Good afternoon. For the record, my name is Vance Burghard. I was diagnosed with ALS in December of 2017. I've been a

participant in the CENTAUR trial since March of 2018. I am not being compensated for my testimony, nor do I have any financial interest in the company. I apologize for my voice. It's very soft due to a non-ALS related viral infection that has affected my vocal cords.

At the time of my diagnosis in '17, I was experiencing extreme weakness in my arms, as well as my hand-grip strength. I was having hand tremors, which made it necessary to use two hands to hold a cup of coffee. Dressing was extremely difficult. I needed assistance to pull up my pants, and zipping them required help or adapted tools. I could not get my arms up high enough to put a T-shirt on by myself.

Eating had also become difficult. I had to have my food cut for me. I was also experiencing muscle twitches in my lower back, upper arms, neck, with drumming in my ears. Walking had become extremely difficult, and I required a wheelchair to get to my appointments throughout the Mayo Clinic during my diagnosis in December. I was fitted for

a leg brace at the time to help address the foot drop. I had to stop working in my store because I no longer had strength or stamina, stock shelves, or help customers. My wife had become my caregiver to help me through the day.

On the return home from Mayo, I was put on prescriptions of riluzole and for Radicava. I was asked by my neurologist at Oregon Health Science University if I'd be interested in participating in a clinical trial for a new drug. I then began the clinical trial of AMX0035 in March of 2018.

My first strength assessment found a grip strength in my hands of 18 pounds. My arm and leg strength were both extremely low. I started to notice an improvement in my strength and mobility by June 2018. In August, I drilled a 100-square feet deck, digging post holes, mixing and pouring concrete, and cutting the lumber and attaching the deck.

My wife and I also began to travel again, and I no longer needed a wheelchair around airports, although I was still using my brace. By

the end of the year in 2018, I was able again to work and oversee the daily operation of my business and continuing to teach my daughter, who now owns the business, its operation.

This drug has greatly improved my quality of life and that of my wife, children, and grandchildren. In 2018, '19, and '20, we were again regularly traveling. We've walked many miles, in Europe, in the Great Wall of China, and ascending the stairs to Potala Palace in Tibet. Three years ago, I would never have thought this.

My health and strength seemed to have stabilized. Although I am not back a hundred percent, grip strength is now 70 pounds in both hands. I am no longer using a foot brace and fully independent and capable of living a quality life, enjoying times and travel with my family.

AMX0035 for me is a life-saving and life-changing drug. I ask that you quickly move forward in approving the treatment of ALS so that others affected with this disease [indiscernible.]. Thank you.

DR. MONTINE: Thank you.

Speaker 3, your audio is now connected. Will you begin, please, by introducing yourself? Please state your name and any organization you are representing for the record.

(No response.)

DR. ABRAMS: Hello?

DR. MONTINE: Speaker 3, you may be muted.

(No response.)

DR. MONTINE: Hello again. Speaker 3, this is Tom Montine. If you can hear me -- I can't hear you. I don't think any of us can hear you, so you may still be muted.

Hello?

DR. ABRAMS: Hi. This is Dr. Abrams. Am I connected now?

DR. MONTINE: You are. Thank you. Please go ahead.

DR. ABRAMS: Okay. Forgive me for the misconnection there.

DR. MONTINE: No problem.

DR. ABRAMS: Good afternoon, everyone. I'm

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

At present today, we oppose FDA's approval of AMX0035. 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, as we've heard. Summary statistical values were marginal; primary endpoint effect sizes modest; dropout rates high; and statistical modeling questionable.

The sponsor disregarded the FDA's recommendation to use joint rank analyses of function and survival. Analyses of secondary endpoints did not show any benefit. As with many small trials, of course, group imbalances and baseline disease characteristics, and post-enrollment initiation of other drugs plausibly compromised this study's validity and may have biased the primary efficacy results.

The subsequent open-label extension study,

according to FDA scientists, was, quote, "difficult to interpret," and, quote, "not persuasive" because of its open-label design and also because of substantial dropout rate and flawed statistical analyses.

Per the FDA's penultimate briefing statement in the briefing packet, the agency may rely on, quote, "a single large multicenter trial to establish effectiveness," close quote. However, the FDA also has appropriately stated that such reliance should, quote, "generally be limited to trials that demonstrate a clinically meaningful and statistically very persuasive effect," close quote, which was not the case with this drug, AMX0035.

Notably, in 2017, the FDA published a report documenting numerous cases of favorable phase 2 clinical trial results that were not confirmed in subsequent phase 3 trials. Unfortunately, such a scenario is highly likely for AMX0035.

In conclusion, there is lack of substantial evidence of effectiveness for AMX0035 for treating ALS. The FDA must wait for the results of an

ongoing phase 3 trial before considering approval of this drug. We thus urge the advisory committee today to vote no on the key question before you.

Finally, although the FDA has, quote, "long stressed the appropriateness of exercising regulatory flexibility to drugs for serious diseases," such as this one, "with unmet need," it must do so, as the agency has also said, quote, "while preserving appropriate assurance of safety and effectiveness." In this case we believe such flexibility is unacceptable given the lack of assurance of effectiveness. Thank you.

DR. MONTINE: Thank you.

Speaker 4, your audio is now connected. Will speaker 4 please begin by introducing yourself. Please state your name and any organization that you are representing.

MS. BALAS: Good afternoon. My name is Calaneet Balas, and I'm the president and CEO of the ALS Association. I want to thank you for the opportunity to provide public comment today regarding the new drug application for AMX0035.

I'm here today speaking on behalf of over 20,000 people living with ALS and their loved ones that the association represents, asking the committee to recommend AMX0035 for FDA approval.

We are an initial funder of Amylyx's CENTAUR trial. We have committed $2.2 million to the research behind AMX0035, and we stand to be repaid up to 150 percent of our investment through a standard repayment clause, all of which will go back into our research program to invest in more research. But we would be here today for any potential ALS therapy that is safe and offers clinical benefit.

Based on all the evidence we've seen, AMX0035 is both safe and effective. As FDA acknowledged in its 2019 ALS guidance, people with ALS are willing to accept greater risk both in terms of safety and uncertainty of benefit given the devastating nature of this disease. Thankfully, in the case of AMX0035, the question of safety has been answered, as it includes two already pre-approved compounds with known safety

profiles.

As for effectiveness, AMX0035 has been shown to slow down disease progression, and as you know, the open-label extension study showed several months of increase in survival. Some might not see several months as meaningful, but as you have heard from the ALS community, including at our We Can't Wait meeting last May, several months is very meaningful, especially when the average life expectancy after diagnosis is 2 to 5 years. That could mean an opportunity to attend a wedding, a graduation, or see a new birth.

We have included comments from people with ALS and their families in our written comments and strongly encourage you to read them. There's no ethical or scientific justification today to delay access to AMX0035 for people living with ALS. AMX0035 complements and does not duplicate any other ALS treatment. Every year of delay in approval will result in thousands of life-years lost.

We also believe the FDA is asking the wrong

question today. The question appears to overlook the agency's guidance that the speed and severity of ALS and the few treatment options available are relevant. A better question would be, do we know enough about the safety and effectiveness of AMX0035 to make it a treatment option for people living with ALS today? To which the answer would be a definitive yes.

We all want certainty, but the only certainty today is that ALS is cruel and it is fatal. So I ask the committee to consider this. Given the strong safety record of AMX0035 and the compelling clinical benefit for trial participants, is it better to approve the drug immediately and take the chance that a fraction of the people who receive it might not benefit from it, or is it better to recommend to delay the approval and take the chance that thousands of people who want this drug will progress further and potentially die sooner than necessary? The worst outcome in this case is not approving AMX0035.

We believe, based on the science and the

certainty of this devastating and deadly disease, the choice is clear. Please exercise optimal regulatory flexibility and recommend the approval of AMX0035. My ask is the same ask I had in May of 2021. In an unfair, unequal, and unjust world, can we as leaders in different roles in this community lean in and use the FDA guidance and the regulatory flexibility to get safe and promising treatments to people with ALS as fast as possible?

This committee -- you -- have that opportunity today. Thank you again for the opportunity to address the committee.

DR. MONTINE: Thank you.

Speaker 5, you are now connected to the audio. Would you please begin by introducing yourself? State your name and any organization that you may represent.

MR. KOWALSKI: My name is Steve Kowalski, and I have no conflict of interest to disclose, and I am representing no organization. I am 58 years old. I was diagnosed with ALS in 2017. I have three adult children who take turns providing me

with care; if you can see the picture I submitted there in the forefront with me at our first ALS fundraising event back in 2018.

Because of ALS, I retired after 34 years in high-tech. I've been faced with many complex challenges, both personally and professionally. ALS by far is the most difficult and complex endeavor I have ever encountered, however, those that know me well know I never give up. ALS has taken many things, but not my hope, optimism, and determination.

Speaking of optimism, since 2017, I have seen increased funding for ALS research. Conversely, what I don't see is the same progress in ALS drug development coming to market. The FDA 2019 ALS guidance continues to be tested with the submission of AMX0035, particularly exercising regulatory flexibility and applying the statutory standards to drugs for serious disease with unmet medical needs, while preserving safety and effectiveness.

AMX0035 showed benefit with retention of

function and increase in survival. It is safe and well tolerated with minimal side effects. Based on this data and under the care of my neurologist, I decided to compound this treatment myself. I can report the same safety and tolerance results, however, the out-of-pocket costs has financial impact.

The essential question for me is whether the phase 2 data is strong enough for recommended approval or is more data needed from a multi-year phase 3 trial? I believe there is enough evidence for this advisory committee's approval and full FDA approval. Waiting several years is too long. Sadly, many people living with ALS will no longer be with us by then.

That essential question also forces us to put a value on function and survival data. Any additional time with loved ones or function to touch a loved one has a measurable value. Scientists and researchers rightly focus on p-value. What about H value? Human value. More time and function is valuable to every human being.

We know what ALS looks like. We see its devastating physical effects. I want to share my perspective on what ALS feels like. To me, ALS feels like I'm being buried alive. For some it's slow; others, very quickly. Either way it ends in the same exact way, with one final breath.

I want to take a moment to honor those ALS patients who died during the participation in the CENTAUR trial. I will continue to advocate with every breath I have. I ask you to help me make ALS a livable disease until we find a cure. Thank you for your time.

DR. MONTINE: Thank you.

Speaker 6, your audio is now connected. Will you please introduce yourself? State your name and any organization you are representing.

DR. BEDLACK: Hello, everyone. My name is Richard Bedlack. I have an MD and a PhD in neuroscience. I'm currently professor of neurology and director of the ALS clinic at Duke University. I'm also a paid consultant for several companies, including Amylyx. I'm not being paid anything for

my testimony today, and the viewpoints I'm expressing are my own.

Over the past 21 years, I've helped design, conduct, monitor, and review studies on dozens of experimental ALS therapies. The vast majority showed no benefit. ALS research is difficult. My other job, it's even harder. I've been a neurologist for more than 3,000 people with ALS. Sadly, I've had to watch most of them become rapidly disabled and die prematurely with no effective treatment.

In my opinion, the trial of AMX0035 was well designed and well conducted. I understand that it has some minor flaws, but every trial does. The most serious criticisms of the review committee I believe were thoroughly debunked by Dr. Shefner in his recent presentation.

The best available ALS outcome measures, ALSFRS-R progression, and tracheostomy-free survival were utilized, and these were analyzed in exactly the right ways. The conclusions published in two of the world's most prestigious peer-

reviewed medical journals are justified. This drug slows disability and prolongs survival to statistically and clinically significant degrees, and it appears safe.

I understand the scientific desire to replicate these results in another trial, however, another trial will take three years, during which time half of the 20,000 Americans currently living with ALS will die from it. If the FDA can employ conditional approval for an Alzheimer's drug that has not yet shown clear clinical benefit, why can't this pathway be employed to get AMX0035 into the hands of people living with ALS while the confirmatory study is conducted?

One of my patients once described ALS as follows: "It's like I'm living in a box. Every day it gets smaller on all sides, further restricting my movements. One day it's going to get so small and tight that it's going to crush the life out of me."

Imagine if that was you or your loved one facing that horror. After reading the

peer-reviewed publications on the AMX0035 trial, wouldn't you want access to this drug, even if its benefits have not been confirmed in a second trial? I know I would. Thank you.

DR. MONTINE: Thank you.

Speaker 7, your audio is now connected. Would you please begin by introducing yourself? Please state your name and any organization you may represent for the record.

DR. ZUCKERMAN: I'm Dr. Diana Zuckerman, president of the National Center for Health Research. We scrutinize the safety and effectiveness of medical products, and we don't accept funding from companies that make those products. My expertise is based on my post-doctoral training in epidemiology and public health, and as former staff at HHS, and a faculty member and researcher at Yale and Harvard.

ALS is a devastating disease, and all of us want better treatments to be available as soon as possible, but today's question is different. Do the data from these two studies support a

conclusion that AMX0035 is an effective treatment of ALS? Your vote will set a precedent for other FDA decisions just as FDA's approval of Aduhelm set a very unfortunate precedent, where science was ignored, delaying the research evidence that patients need and deserve.

AMX0035 combines Turso and PB, and Turso alone was very effective for ALS patients in a small pilot study, and a large study of that same supplement will be completed this year. You can see it on clinicaltrials.gov. Meanwhile, any patient can buy Turso for 47 cents a pill on Amazon. Why not wait till that study's done since there's no clinical evidence supporting PB?

Now let's focus on the strengths and weaknesses of the sponsor's two studies. The biggest problem with the open-label extension is that it had no control group, and most patients dropped out after a year. Only two patients completed treatment. That tells you that there's a serious problem with AMX0035. We agree with the FDA that the extension data don't support approval.

The RCT had one terrible flaw. FDA advised the company to create a combination measure of function and survival, but the company refused, and when looking at the survivors, many patients in the experimental group had stopped taking AMX0035, so they should not have been counted as AMX0035 survivors. In fact, there were five deaths among AMX0035 patients and two in placebo. Since the placebo group was half as big, that means approximately equal mortality in both groups.

Here are just a few of the other flaws: a small change in the primary endpoint, but almost 1 in 5 patients didn't complete that measure; 95 percent of patients were white compared to 75 percent with ALS in real life; and the question about whether the test was really blinded. We agree with FDA that the secondary endpoint results are not compelling or supportive of the primary endpoint.

In conclusion, Turso looks promising for ALS and it's already available on Amazon for 47 cents a pill. A large multicenter clinical trial will be

completed this year. Why not wait till that study is done and also consider interim results of the sponsor's larger study of AMX0035 when there are enough data to find out if their drug really works? Thank you so much.

DR. MONTINE: Thank you.

Speaker 8, your audio is now connected. Would you please begin by introducing yourself? Please state your name and any organization that you represent for the record?

(No response.)

DR. MONTINE: Speaker 8, you may be muted. We're not hearing you.

MS. B. MOUREY: My name is Becky Mourey, and I am living with ALS. Thank you for the opportunity to speak to you. ALS is stealing my voice -- [indiscernible].

MS. A. MOUREY: "Do you remember those inflatable punching bags many of us had as kids? Once struck, it would bounce back up, just to be hit again, and again, and again. This is what living with ALS is like. Out of the blue, it

strikes.

"My first gut punch was in June of 2020 with weakness in my right index finger. At this time, I was regularly enjoying trail runs in the woods near my home. My profession as a musician and private music teacher was still a huge part of my life and my identity. As summer progressed, so did my symptoms. In October of 2020, an EMG was deemed concerning for ALS. By then I had already taken a hard fall on a run and had to transition to walking. My fingers were suddenly too weak to seal the key holes on my clarinet. Running and music were now in the past.

"With each strike, people with ALS are forced to grieve another loss, process that loss, pivot and adapt, only to be struck again, and again, and again. Much like that armless toy punching bag, people with ALS have almost nothing to fight back with.

"You're an advisory committee. You're here to consider whether or not the data from the CENTAUR trial is worthy of your recommendation for

approval of AMX0035. I am here to tell you it is. The CENTAUR trial met its primary outcome on a trial design approved by the FDA. It showed a slowing of progression and loss of function, as well as an average increased survival of 6 and a half months. It is the first ALS therapy to both increase survival and slow loss of function.

"AMX0035 has outperformed the two mediocre therapies currently on the market. It has proven to be safe. The most common side effects are GI related. When facing the horrific death that ALS dictates, considering constipation and diarrhea adverse effects is almost comical.

"AMX0035 is a combination of sodium phenylbutyrate, a drug approved by the FDA in 1996 to treat a urea disorder in infants, and Tudca, a supplement you and I can order on Amazon and have tomorrow. People living with ALS have wanted this drug since the day the positive results became public in December 2019, well over two years ago. To deny us access is cruel.

"While waiting to gain access to AMX0035, I

have gone from being a fiercely independent person to being dependent on others for the most basic needs. Because the components are so readily available, people, including myself, are taking them off label. But this is not the same as having access to AMX003535, and it presents real safety and equity issues that approval would solve. It is quite expensive, not compounded the same, and its supplements are not regulated. It is not pharma grade.

"Approving and regulating AMX0035 is the best way to serve the ALS community and to protect us. Because I am on PB off label, I am excluded from participating in clinical trials of investigational therapies. The sooner AMX0035 is made standard of care, the sooner I and everyone else on PB can get back to lending ourselves to science.

"We deserve a chance to see if AMX0035 will give us a reprieve in between hits. Slowing down the loss of function is significant to me and my family. More time to tell my children I love them

with my own voice is everything to me. Eating with my family and tasting every savory morsel for a little longer before losing my ability to swallow directly equates to quality of life."

MS. B. MOUREY: [Indiscernible] -- to recommend the approval of AMX0035. Thank you.

DR. MONTINE: Thank you.

Speaker number 9, your audio is now connected. Would you please begin by introducing yourself? Please state your name and any organization that you represent.

MR. GOLJI: Hi. My name is Javad Golji. I'm here to testify on behalf of myself, my wife, Christina who has ALS, and my three children. I do not work for Amylyx or any of its competitors. I have no financial relationship with them. I do drug discovery research in the oncology space, but today I'm here to testify as a patient's family.

Christina was diagnosed with ALS 5 years and 6 days ago at the age of 31. At the time of her diagnosis, she was given two years to live. One of the first things we did once we had diagnosis was

go explore, look for, and find upcoming and promising clinical trials, anything that would help overturn this death sentence.

Christina joined the AMX0035 clinical trial as patient number 1, and she has been on the open-label extension until today. From our experience, AMX0035 has played a big part in delaying -- 2-year to now 5 years and running -- Christina's private life with ALS and delaying the progression of disease. Two times throughout this time, Christina took a break from taking AMX0035, once between the end of the trial and the start of the extension, and once again before the start of the open extension, and during both breaks we noticed a measurable increase in her disease progression.

The way Christina's ALS has progressed, there have been periods where she has lost yet another one of her abilities: first, her ability to use her hands; then her ability to walk; then her ability to stand; and finally in the last year, her ability to speak and to breathe on her own. In

between these periods of loss of ability, there have been plateaus, and those have been priceless for our family.

Over the last five years, my youngest has grown from the age of 4 to 9, my daughter has grown from the age of 6 to 11, and my eldest son from the age of 8 to 13. For three of those years, Christina could walk, and she was able to join the kids and myself for a trip to the Yellowstone and Smoky Mountains. For four of those years, she could speak and use her own voice to tell my 6-year-old son how much she loved him every day. Every additional day that Christina has, every additional lengthening of the plateau, is priceless. It's an additional day for her kids to see her smile and for them to sit next to her and watch TV with her.

The cure is a perfect dream, but even without a cure, any delay in disease progression has a tremendous impact on families like ours, and it's priceless. I urge the FDA consider the effectiveness of AMX0035 as meaningful and

priceless to patients' lives, and to consider this urgently. Thank you.

DR. MONTINE: Thank you.

Speaker number 10, your audio is now connected. Would you please state your name and any organization you represent for the record?

MR. CANTER: Thank you for letting me speak. My name is Greg Canter. I am 42 years old, and I do have ALS. I have no financial obligation or a gain from speaking at this meeting. I'm speaking on behalf of all those who have ALS and those who have no longer a voice.

My story started October 2018 when I was first diagnosed. In the midst of desperation, I quickly looked for a clinical trial to get into. I had no other medical option. The only other option I had available was a standard regimen of riluzole, magnesium, and other supplements.

January 2019 was my life-saving move when I got into the CENTAUR AMX0035 clinical trial. I barely qualified. Without getting into this trial with only riluzole and supplementation, I would

already be in the ground.

January 2019 is when the trial started, which was a placebo-based trial and went through the end of June. At the end of June, my testing numbers were at 44 percent opposed to 60 percent when I entered the trial, doing a quick decline in my lung function. Without ever being told, I personally believed that I was on the placebo. In July, I was offered the open-label extension of which I was then guaranteed AMX0035.

Now, fast-forward, and here I am, 2 and a half years later, and my numbers are still regulated around the 40 percent mark. If I would have continued on that initial steep decline, respiratory failure would have come quick. This is the reason I say my data speaks for itself. This is not an opinion because that is why I'm still here alive today. Since I began the trial in January 2019, I have yet had any adverse side effects. To me, this drug is proven itself safe and effective.

Let me leave you with this. You can plan a

vacation next year. You can plan to be alive next year. I can't. I can't take anything for granted. The two drugs in AMX0035, neither are a new drug. AMX0035 is shown to be safe. I'm evidence of that. I've had no adverse reactions. It's effective. I'm evidence of that as well. In fact, I did a counting test in November 2020 to see how far I could count in one breath. I got to 66. Fast forward 2 and a half years later, 3 weeks ago, I counted to 67 during my appointment with my ALS specialist. This is just a portion of my data.

From my experience in both the randomized trial and the open-label extension, it shows that AMX0035 is effective in the treatment for patients with ALS like myself, and I firmly believe, in the year 2022, ALS should be a treatable disease. Thank you.

DR. MONTINE: Thank you.

Speaker number 11, your audio is now connected. Please state your name and any organization you represent for the record.

MS. PAULS BACKMAN: Good afternoon. I am

Andrea Pauls Backman, the CEO of the Les Turner ALS Foundation. My only disclosure is that the Les Turner ALS Foundation receives less than 2 percent of all annual revenues from pharmaceutical companies, including Amylyx Pharmaceuticals. We are grateful to this advisory committee for your dedication to reviewing the science and hearing from the ALS community regarding AMX0035.

My mother Sally died from ALS in 2010, so I come to you today not only as a patient advocate, but as a grieving daughter. I bring both my professional and my very personal passion to my remarks today.

The Les Turner ALS Foundation is the oldest independent ALS group in the country, so for 45 years it has been our mission to provide the most comprehensive care and support to people living with ALS and their families so they can confidently navigate the disease, and for 45 years, we have advanced scientific research for the prevention, treatment, and cure of ALS.

Each year at the foundation, one-third of

the people we directly serve die from ALS. This month I attended the funeral of an 18-year-old boy who we lost within a few short months to a very rapid form of this disease. No parents should have to bury a child this way.

The photos you see on the screen represent some of the thousands of people we've had the privilege to serve for our personalized services. ALS can affect anyone, anywhere, at any time. These are the faces of ALS.

We only have two drugs approved by the FDA to treat ALS. We desperately need more options. We have no time to waste to approve AMX0035. AMX0035 is the first ALS therapeutic to demonstrate both a statistically significant survival and functional benefit in ALS. There is no safety signal in AMX0035, and the adequacy and clinical meaningfulness of the data was clearly demonstrated in a well-designed, robust, randomized-controlled trial at 25 top clinical trial sites in the U.S.

AMX0035 is not perfect, but it is effective in the treatment of people living with ALS.

AMX0035 has been shown to slow ALS disease progression by 2 points on the ALSFRS scale and extend life by 6 and a half months. These numbers may not sound like much, but for people who lose their lives within an average of 2 to 5 years, slowing progression extends the precious time families have together. Slowing the disease progression means more graduations, more weddings, and more family holidays. It means cutting up your own food, speaking on your own, and even breathing on your own. It means more time with those you love. We have no time to waste.

As these faces of ALS and thousands of others attest, there is an urgent need for access to safe and effective therapies and regulatory flexibility for unmet medical needs in ALS. We urge the FDA advisory committee to recommend full approval of AMX0035. There is no other moral choice. We have no time to waste. Thank you.

DR. MONTINE: Thank you. [Inaudible - audio gap].

MS. THOMPSON: Hello. My name is Christa

Thompson. For the record, I am not being compensated in any way by Amylyx for this testimony, and I have no other conflicts of interest to disclose. My husband Owen was diagnosed with ALS in 2018 at 47 years old. He was in the CENTAUR trial at Mass General Hospital, and then began taking AMX0035 through the company's open-label extension.

I am here to testify that this treatment has slowed Owen's progression, and I ask you to fully support recommendation of approval by the FDA. I support approval because AMX0035 is safe, and it works. Owen has been taking it with no side effects for over two years, twice a day, every day. While it has been devastating to watch Owen's inevitable loss of function, we have largely been able to stay one step ahead of the disease progression with the help of this treatment.

Why does this matter? Because staying one step ahead is being able to get the power wheelchair before it's needed. Two points in 6 months gave Owen more time to finish recording

his voice so that our three boys don't have to try to remember what their dad sounds like when he says, "Good night, Bud. I love you." That's what 2 points in 6 months means. Our sons can still hear his voice.

My family of five future has been shattered by ALS, however, I am thankful that Owen has the rare opportunity to take this drug so he can leave a longer legacy. Last June, our oldest graduated from high school. Not only was Owen able to go and be at the ceremony; he didn't need a BiPap mask because AMX0035 slowed his progression. So the legacy of that day is just a dad's proud smile, a smile not hidden behind a breathing machine. That is forever the memory, the moment, the unobstructed smile.

All people with ALS deserve this. That is what slowing progression means to this community. It also means a 50th birthday party at Fenway Park this past August. It means my husband, who I met at summer camp in 1987, can still smile at me when I walk in a room. Seeing and keeping that smile

for longer means everything.

ALS is a complex and challenging diagnosis and disease, so the path to treatments and cures is also challenging and complex. What is not complex is that AMX0035 is safe and well tolerated. It is not complex that extending life and slowing progression means more ALS families like mine get the chance to have longer legacies and more smiles. It means we get more moments.

Please address the unmet need for ALS treatment and recommend AMX0035 for full approval by the FDA. Thank you so much for this opportunity to speak to you today.

DR. MONTINE: Thank you.

Speaker 13, your audio is now connected. If you would please state your name and any organization you may represent.

MS. PETERSEN: Thank you. My name is Gwen Petersen. I am living with ALS. I'm not representing any org. I have consulted for several pharm companies in ALS drug development, including Amylyx. I am not being compensated in any way by

Amylyx for this testimony today. My voice, as slow and as frustrating as it is compared to what it used to be, is a gift, especially five years living with ALS. I will continue to use my gift as a voice for the voiceless.

I was diagnosed with ALS at 32 years old. It was less than one year after marrying my best friend; no family history, no genetic mutations found. If I can get ALS, anyone can get ALS. I was not a participant in the AMX0035 trial, however, I did participate in a year-long clinical trial with an experimental ALS therapy.

I so vividly remember the study consent process and the research nurse who placed strong emphasis on the following words. She said, "You may not receive any direct benefit from taking part in this research study. Others with ALS may benefit in the future from what we learn in this study."

I have invested a lot. I have taken risks. I had 7 lumbar punctures with a 50/50 coin flip of getting placebo, and I did it for the next

generation of people living with ALS. Advisory committee, please recommend AMX0035 for full approval as therapy that has a good safety profile, met its primary endpoint, and is efficacious for this generation of people living with ALS.

My slide up on the screen is what I would miss out on in 6 and a half months. On the left, that's me. Advocacy is a huge part of my life, and we showed you a lot in 6 and a half months. On the right, those are my nieces and nephews. ALS robbed me and my husband of having our own kids. That never is going to be easy to say. On the bright side, though, I get to be the favorite aunt.

I ask the committee to go home tonight after this presentation and ruminate on this. What does 6 and a half months mean to you? What would you miss in 6 and a half months? Thank you.

DR. MONTINE: Thank you.

Speaker 14, would you please begin by introducing yourself? State your name and any organization that you may represent.

MS. BYRD: I am Katrina Byrd. I am not

being compensated in any way by Amylyx for this testimony, and I have no other conflicts of interest to disclose. Thank you, FDA and the advisory committee for this opportunity.

In a hospital room in Jackson, Mississippi, Dora, my partner of 23 years, coughed vibrantly in the flat hospital bed. She struggled, unable to use her hands to sit up, unable to press the call button, unable to reach out to me. For months, her breathing was labored as her speech and swallowing deteriorated. Her gasps for air overshadowed the two feeding machines beeping as it dispensed formula into her newly installed PEG tube.

The tech, who flattened the bed to administer an EMG test, was confused. I pressed the call button, then lifted Dora to a sitting position. Several nurses entered and watched as I steadied Dora with one hand and gently rubbed her back with the other. She continued coughing unable to clear her lungs.

"I can't do nothing," our assigned nurse said when she realized the phlegm was in the lungs

and not in the mouth. "She ate too much pudding." "She hasn't eaten anything today," I said, as I continued rubbing Dora's back. "Well, maybe you stepped away," she said. "I've been by her side all day." She pulled up Dora's chart on the computer, and then said, "Oh. I guess she didn't have anything to eat today." Later that day, I learned that it is unsafe to lay flat while tube feeding because the patient may aspirate.

Diagnosed with ALS November 18, 2019, Dora passed away 76 days later on February 2, 2020. As her sole caregiver, I watched her die daily, our journey a circle of disparity; no skilled nursing care, no ALS clinic, no equipment. With no money and no legal ties to one another, we pushed forward, nothing between us but prayers, tears, and wishes.

For us, 2 points on the ALSFRS scale means morning tea on the front porch; safer trips to the bathroom; picking daffodils from the yard; less drooling; visiting her son's grave; laughing without choking.

In the land of the free, how do you recognize ALS caregivers? They are bound by a life of labored breaths, tube feedings, and slow, calculated steps to the bathroom. They are broken by the phrases, "There's nothing I can do. Take her home and keep her comfortable." I am haunted by Dora's last three words spoken with great effort and difficulty, "I love you."

Please recommend the approval of AMX0035. Thank you.

DR. MONTINE: Thank you.

Speaker 15, you're now connected. Would you please introduce yourself by stating your name and any organization that you may represent for the record?

MR. MELMEYER: Thank you for the opportunity to speak today. I am Paul Melmeyer, vice president of Public Policy and Advocacy at the Muscular Dystrophy Association, and we serve all individuals with neuromuscular diseases, including ALS, in a variety of ways, including advocating for the accelerated development of more and better

therapies for the neuromuscular disease patient population. I have no financial relationships to mention.

The Muscular Dystrophy Association does not participate in product-specific advocacy, and thus will not make a specific recommendation on this drug. Instead, I will outline the flexible regulatory approach we expect the FDA and this advisory committee to utilize when considering this and all rare neuromuscular disease therapies. We are grateful the FDA mentioned exercising appropriate regulatory flexibility this morning, and I encourage this committee to remember the following three key points when evaluating this and all other neuromuscular therapies.

First, we encourage FDA and the advisory committee to consider all the ways of demonstrating substantial evidence of effectiveness, including through the use of one adequate and well-controlled clinical investigation plus confirmatory evidence.

As outlined in its December 2019 guidance, FDA states that the agency, quote, "will consider a

number of factors when determining whether reliance on a single adequate and well-controlled clinical investigation plus confirmatory evidence is appropriate, including the seriousness of the disease, particularly where there is an unmet medical need; the size of the patient population; and whether it is ethical and practicable to conduct more than one adequate and well-controlled clinical investigation," end quote.

Second, we remind the FDA and the advisory committee of flexibilities outlined in the ALS Developing Drugs for Treatment Guidance, including that the, quote, "FDA will consider patient tolerance for risk in a serious and life-threatening nature of the condition in the context of statutory requirements for safety and efficacy," end quote, and, quote, "FDA has long stressed the appropriateness of exercising regulatory flexibility in applying the statutory standards to drugs for serious diseases with unmet medical needs while preserving appropriate assurance of safety and effectiveness," end quote.

Finally, the FDA has a well-established record of approving treatments for serious and life-threatening rare diseases without the standard level of proof of effectiveness required in more common or less serious diseases. Analyses have shown that at least two-thirds of rare disease drug approvals are done so by the agency, flexibly considering whether the effect in this evidence is adequate. These flexibilities have been reiterated by FDASIA, FDARA, and consistently supported by patients, their loved ones, the organizations that serve them, their clinicians, and their elected officials.

Developing treatments for rare neuromuscular diseases presents unique challenges that must be addressed with the previous mentioned flexibilities. Today, we are asking the FDA reviewers and this advisory committee to remember these flexible approaches already put forward by the agency when evaluating this and all new potential treatments for ALS and rare neuromuscular diseases. Thank you.

DR. MONTINE: Thank you.

Speaker 16, your audio is now connected. Would you please begin by introducing yourself, stating your name and any organization that you may represent?

DR. BERRY: Thank you for having me today. My name is James Berry. I'm a neurologist, and for over a decade I've been an ALS clinician and clinical researcher at the Healey and AMG Center for ALS at Mass General Hospital. I'm the chief of the Division of ALS and director of the Neurological Clinical Research Institute, and co-chair of the NEALS network nationally.

I was a Mass General site investigator for the CENTAUR trial of AMX0035 and for the ongoing PHOENIX trial, and the Mass General Neurological Clinical Research Institute acted as the clinical research organization for the CENTAUR trial. I have no other affiliation with Amylyx, and my comments today are my own.

Given all that you've heard in the advisory panel today and the comments during this public

session, I'll spend very little time rehashing the remarkable unmet need for people with ALS, but suffice it to say that the need is pressing and, unfortunately, many of the potential therapies that we test in trials do not measure up. But today is an exciting day because today we're talking about a therapy that has measured up in trials.

AMX0035 was tested in a rigorous, well-designed, carefully conducted RCT using standard and accepted clinical outcome measures with clear clinical meaning. The slope of decline in the ALSFRS-R was prospectively designated as the primary endpoint in the trial of AMX0035, and survival was also analyzed.

To be sure, the primary endpoint was not the combined assessment of function and survival or task joint rank. As the primary author of a paper illustrating the application of task joint rank in ALS clinical trials, I know its potential benefit in a long trial expected to see large numbers of survival events, as well as decline in the ALSFRS-R. But in that manuscript, we also noted

that in shorter trials, enrolling people early in the disease, like the CENTAUR trial where the number of survival events is expected to be low, and was, the task analysis is subject to a higher rate of type 2 error than an ALSFRS-R slopes analysis, thus falsely declaring an effective therapy to be ineffective, the worst error we can make for a safe therapy in a fatal disease.

In short, the CENTAUR trial of AMX0035 in people with ALS was a high-quality RCT using appropriate endpoints and an appropriate rigorous analysis. It demonstrated efficacy in prespecified analyses, and it showed the safety of the combination drug, both components of which are available on the market.

Finally, a large phase 3 trial is already ongoing, so more data will become available soon as you've heard. Why not wait for that trial to complete? Because on balance, there is compelling trial evidence today to approve the drug as we await those results, and because inaction today will delay a decision by years, during which a

generation of people with ALS will die while we wait for our confirmatory evidence. The agency allows for a single trial approval, and this would be an appropriate use of that guidance. Thank you.

DR. MONTINE: Thank you.

Speaker 17, your audio is now connected. Would you please begin by introducing yourself, stating your name and any organization you represent?

MR. GREEN: Hi. My name is Phil Green. By way of disclosure, Sandy Morris and I are both members of the Amylyx Patient Advisory Council, and we are not being compensated for this testimony.

I'm a 52-year-old father of four wonderful children, one of which turns 20 today, and a husband to the most amazing wife. I like many others participated in the Ice Bucket Challenge, but it is fair to say that at time, I was oblivious to ALS and the devastation it leaves in its way.

That all changed on August 29, 2018, when I was diagnosed with ALS. My particular ALS presented with weakness in my hands, as I was

unable to muster enough strength to even clip my fingernails. Within 2 months, I found myself struggling to button my shirts, and within 5 months, I was completely unable to button them. If I had access to AMX0035 three years ago, maybe I would still be able to take my pills 4 times a day on my own or feed myself. These are simple but significant events in my daily life that I now have to rely on someone else to help me with.

We support the approval of AMX0035, based on the phase 2 results. In ALS, we don't have many options that change the trajectory of our disease. Those of us living with ALS deserve to try anything that is safe and that may maintain function and extend time with our loved ones. Those of us living with ALS don't need complicated statistics and a p-value to want to try something that might help. We know that ALS is heterogeneous, and the treatments that work for some may not work for everyone, but we truly have nothing to lose.

In the briefing document, FDA acknowledges that the pathophysiology of ALS is not well known

and likely involves multiple processes and pathways. I can't help but feel like we are applying high precision statistical analysis to our closer and fuzzy understanding of ALS. People are dying while treatment after treatment has failed to meet clinical endpoints because of our poor understanding of this disease, and yet this therapy, AMX0035, did meet its endpoints.

AMX0035 experts and patients alike know that what we need is a toolkit of possible therapies. As an advisory committee, you have the opportunity to bring humanity to the science of ALS drug development and recommend that the FDA exercise its regulatory flexibility and approve AMX0035 for all people diagnosed with ALS. We are human beings after all, not statistics, not numbers.

MS. S. MORRIS: I'm Sandy Morris, and I was diagnosed with ALS on January 6, 2018. As you [indiscernible], destructive disease. My daughter, Kylan, will help with me with my words. We are here today to ask you to recommend the approval of AMX0035.

MS. K. MORRIS: "We're an ALS family of five. My parents have been in love for 33 years. Mom lost her ability to walk within 7 months after diagnosis. We're doing our best as an ALS family.

"AMX0035 has shown in their trial that people living with ALS can live six extra months. I can't even begin to tell you what it would mean to my family to have my mom for six more months. Six more months, and my mama would see my 25th birthday, my baby brother's 21st birthday, my middle brother's 23rd birthday, and we get to celebrate 28 years of marriage with my dad.

"Should AMX0035 not get approved now, approximately 20,000 Americans with ALS will die brutal deaths before the phase 3 trial is completed. We will knowingly wipe out an entire ALS generation, ignoring their pleas for the chance at another 6 months. Don't let this happen to our family. What you need to know is this. People living with ALS understand that a therapy might not work for everyone in this heterogeneous disease. What we cannot accept is having zero options in a

100 percent universally fatal disease."

MS. MORRIS: My apologies for my compromised voice. Maybe if I had been allowed to take AMX0035, you would be able to hear me more clearly. We are human, not lepers. Thank you.

DR. MONTINE: Thank you.

Speaker number 18, your audio is now connected. Please begin by introducing yourself, stating your name and any organization you represent.

MR. REYES: Hello. I am Juan Reyes. I have no organizational or financial disclosures to declare. I reside in Texas with my family and have been living with ALS for over six years. I would like to thank the FDA and the advisory committee for the opportunity to speak today on behalf of my family and the many others who stand to benefit from this treatment.

As a retired United States Air Force veteran, husband, and father of four beautiful children, three of which are adopted, I need access to treatment now. Having lived beyond the window

of opportunity for any potential clinical trial, I am without options. I am, in fact, at your mercy for any life-extending treatment. Additionally, as a veteran, I and most veterans are without pathways to experimental treatment through the VA itself. This is especially tragic because veterans are at least twice as likely than the civilian population to develop ALS.

One veteran who did participate in the Amylyx trials is Jeff Sarnacki, who unfortunately passed in May of 2020. He had just turned 60. Jeff and his wife Juliet approached life voraciously, even with ALS while taking the active drug. Jeff went deep-sea fishing, whitewater rafting in Canada, and took in Red Wings Oggi in college football games. He and Juliet saw the Rolling Stones, Queen, and Bob Seger live in concert, all due to AMX0035.

The AMX0035 trial data show a 6-month extension in life and slowed progression by 2 points on the ALSFRS-R scale. There are those that would and have conveyed to you, no and not

[indiscernible]. To them I say, "Try living with the specter of ALS on your back." Our community, those living with and affected by ALS, have literally communicated our desire for this treatment in the hundreds of comments submitted to you. We understand the risk. We understand the data. We want access now.

Six and a half months or 2 points may not mean much to you, but to me it means another birthday, anniversary, or celebration. It means holding my wife's hand. It means being able to walk my daughter down the aisle at her wedding next year. What would these figures mean to you if you were living with an untreatable, incurable disease? Currently, my ALS clock cannot be stopped, but you can help slow it down. Please recommend AMX0035 for approval now. Thank you.

DR. MONTINE: Thank you.

Speaker 19, your audio is now connected. Would you please begin by introducing yourself, stating your name and any organization that you represent?

MS. DALLE PAZZE: My name is Laura Dalle Pazze, and I am the CEO of I AM ALS. I have no disclosures. For the past 14 years, I have poured my heart, mind, and soul into service at medical research non-profits. At the core of my work lies a question that could not be more urgent. How do we get safe and effective treatments to people in need as quickly and efficiently as possible?

Through my career, I have contended with three horrendous diseases: Parkinson's, Duchenne muscular dystrophy, and now ALS, conditions that rob people of their physical abilities, their dignity, and their lives. I've worked on developing more rigorous preclinical testing standards to weed out poor drug candidates. I have helped develop and validate more sensitive outcome measures to better tease out a drug benefit. I have used data-driven modeling to improve clinical trials so it doesn't take decades and billions to get help.

Here today is a chance to fulfill a promise made to people with ALS. We will listen to you and

consider your input. We will be flexible and consider data from one controlled study. We will consider the risk-benefit profile of the people who are affected. We will do a better job of using advancements in technology, our understanding of your disease, and regulatory flexibility to get you the help you need. The FDA has said all of this. Here is a chance to put action to those words.

Unlike many neurological conditions under this panel's purview, ALS is not a disease of decades; it is measured in moments like an aggressive cancer. A 2017 JAMA oncology review found that of the 62 cancer drugs approved from 2003 to 2013, the average survival benefit was 3 and a half months. For people facing ALS's median time to death from diagnosis of 2 to 3 years, this drug offers an average of 6 and a half more months on this earth.

Please conduct your review and analysis in the ALS context. Focus on the functional outcome measures and analysis we do have rather than biomarkers and tools we aim to make possible in

years to come. When considering p-values in ALS, remember the heterogeneity of our disease and value this hazard ratio the way the cancer community would.

Please also remember that the testimony from people with ALS is critical to contextualize the data presented today. People living with ALS are experts in how their disease affects their lives and what constitutes meaningful effect. Their testimony delivers tangible examples of what 2 points on the ALSFRS-R and 6 and a half more months actually mean in real life: another baseball game with the kids; the dignity of being able to feed oneself; time to record a grandmother's voice for her new grandchild.

I am sure this panel is concerned about possibly making a type 1 error, supporting a drug that does not work. I ask you to be equally concerned about the danger of a type 2 error, not approving a drug that does work. If we wait for the phase 3 data, three years will pass. That will mean 20,000 presently living with ALS die while

waiting, while an additional 20,000 will be newly diagnosed, decline, and some also die without access to this drug.

This drug is not a cure, but it does not need to be for its effects to be transformative for people living with ALS, and these effects are. You have the opportunity here to help take a step toward making ALS a chronic manageable disease. Please take it.

DR. MONTINE: Thank you.

Speaker 20, you're now connected to the audio. If you would, please begin by introducing yourself, stating your name and any organization you represent.

MR. FALIVENA: Good afternoon. My name is Larry Falivena, and I have no financial conflict of interest.

Imagine one day sitting in a doctor's office and hearing the words, "You have ALS," then being told you have 2 to 5 years to live with no way to stop the disease from taking away your ability to move, talk, eat, and eventually breathe. Imagine

leaving the doctor's office, wondering what would happen to your family, unsure of how much time you have left with them. I don't need to imagine this because I've been diagnosed with ALS and lived these moments.

There are currently very limited options available for ALS patients. Half of us diagnosed with ALS die within three years, and most die within five years, a much shorter time frame than the typical clinical trial. Because this disease is fatal, and because of the devastating nature of its effects, when it comes to making a treatment for this disease available to the patient population, the need for urgency and expediency outweighs any need for being overly cautious.

You may consider this kit therapy to only have modest effects, but 6 months of additional lifespan is significant to someone who's told they only have a couple years to live. And a couple points on my ALSFRS score could be the difference between feeding myself and still walking, or not. Having an effective drug that would slow my loss of

functionality would also reduce my medical costs and reduce the burden on my family.

So what would an effective therapy look like in my life? Well, as you can see in my picture, I have two teenage boys. The approval of this drug means more time to be part of their lives and more time with my wife of 20 years. Even though this treatment may not be the cure we're all hoping for, it will get us a step closer to living with ALS, not just dying from it.

The CENTAUR trial data showed that AMX003535 was not only safe but provided statistically significant slowing of disease progression and extended the lives of the patients. Don't let perfect get in the way of good. You must consider that this treatment is the opportunity to give ALS patients the one thing we desperately need: more time, more time with our loved ones, more time to experience and enjoy the life that's being taken away from us, and more time to discover a cure. And time is something we can't waste waiting for this treatment to go through a long process for

approval.

Making AMX0035 available to patients means that the next person that hears the words, "You have ALS," can also hear the words, "and here's a treatment that can help." They can leave the doctor's office with hope. If you deny approval, the fate of the ALS patients will not change. The disease will progress and many will die. But if you do approve it, it might help. I believe it's worth a chance. I ask that you recommend approval of AMX0035 now, and give the ALS patients hope. Thank you.

DR. MONTINE: Thank you.

Speaker number 21 no longer requests time to speak, so if we could please move to speaker 22. Your audio is now on. Would you please introduce yourself, stating your name and any organization you represent?

MR. RUSSO: Good afternoon. My name is John Russo. I have no conflicts of interest to disclose. I am here with my wife Loretta, who will help me read my comments.

I am a nine-year survivor of ALS. I have never been eligible to join a clinical drug trial due to the fact that I was diagnosed 32 months after my first symptoms. I have dedicated what is left of my life, advocating for others, past and those to come, that have not or may not get the opportunity to live as long as I have with this grueling disease. Yes, I still choose this life, as small and difficult as it may be, and I know that the majority of the ALS community would you do the same.

MS. RUSSO: "I have also engaged with the scientific community, including my service as a consumer reviewer for the CDMRP ALS research program for the past six years, as well as many interactions with drug sponsors and scientists. My journey has led me to many conclusions, the most profound of which is the undeniable spirit and determination of those affected by ALS to live. When we are given this death sentence, there isn't any form of appeal. We are left to deal with our dismal fate, knowing that we will die because of

our inability to breathe.

"We are here today to comment on AMX0035, a drug that has shown meaningful efficacy is generally safe, well tolerated, and is easily taken by mouth or feeding tube. Its chemical components are well known by the FDA. We are well aware of the history of drug study failure recorded for this disease. We also recognize the heterogeneous nature of ALS.

"AMX0035 is no panacea. It is, however, a much needed building block along the scientific journey study leading to a cure. Based upon the phase 2 trial results, immediate approval of AMX0035 will extend the lives of those living with ALS today and change the course of ALS drug trial history positively, as well as provide an opportunity to further analyze its effect on subtypes of ALS."

MR. RUSSO: Loads of us here today, representing the 30,000 ALS patients living in the U.S., are united with respect to AMX0035 approval. Let's please work together to change the course of

ALS longevity starting today. Incremental change is meaningful to us. More time is precious for both of those living with ALS and their family. Thank you.

DR. MONTINE: Thank you.

Speaker 23, your audio is now activated. Please begin by introducing yourself, stating your name and any organization you represent.

MR. KAUFFMAN: Greetings from Palo Alto, California. My name is Scott Kauffman. I'm the chair of the ALS Association, and I have no conflict of interest to disclose.

My son Stephen was diagnosed with ALS 10 years ago when he was just 27 years old, and as a parent I can assure you that it's the worst possible diagnosis you can hear about your child. Imagine me sitting in front of a computer and hoping that my son had cancer, or MS, or literally anything other than ALS.

Today, his ALS has progressed -- more about that world in a minute -- to an advanced stage, but he's been able to live a very meaningful life since

his diagnosis. He married his true love three years in and made me a grandfather three years ago. And just this past summer, he was honored by the Basketball Hall of Fame as an NBA superfan.

Today, the ALS Association is the largest philanthropic funder of ALS research in the world and the only organization that provides a wide range of care services in all 50 states to people living with ALS and their families.

On behalf of Stephen and the entire ALS community, I urge the advisory committee to recommend full approval of AMX0035 immediately. Our organization makes this recommendation based on three important considerations.

First, results from the phase 2 trial clearly show that AMX0035 is safe and effective for people living with ALS. Second, after 24 weeks of treatment, AMX0035 significantly slowed ALS functional progression according to the rating scale used by physicians and researchers. And third, long-term survival data reveals that participants in the open-label extension who

received AMX0035 in the clinical trial lived an average of 6.5 months longer than most who received the placebo.

Now, 6 and a half months might not seem like a lot of time to some of you, but as you're hearing from the remarkable people of ALS presenting today and those who have submitted written comments, every day is another opportunity to make meaning out of their lives, and most importantly to give and receive love.

I'd like to revisit the word "progression" because we often talk about how far someone with ALS has progressed because of negative connotation, but what I'd like to do is shift our community's focus to progress to how far we're advancing the science of new treatments towards killing this terrible disease. And I believe AMX0035 represents the next step in developing life-extending treatment, and even if it just adds six more months of life, it is that 6 months that might be combined with other treatments in the pipeline and new ways of caring for people with ALS, all adding up to a

meaningful impact. Most poignantly, those 6 months could be what allows a son to become a father and a father to become a grandfather.

Please, I ask you to approve AMX0035 immediately. People with ALS can't wait for the completion of a phase 3 trial that could add several more years to the process. The amazing people on this call and all those who make up this community deserve to know that you're committed to making progress towards treating and curing this insidious disease. Please, take action today. Thank you.

DR. MONTINE: Thank you.

Speaker 24, your audio is active. Please introduce yourself, stating your name and any organization you represent.

MR. WALLACH: My name is Brian Wallach.

MS. ABREVAYA: "My name is Brian Wallach. I am a 41-year-old father of two beautiful intelligent 4- and 6-year-old daughters. Five years ago when I was just 36, and on the same day we brought our second daughter home from the

hospital, I was diagnosed with ALS. Since then, I have gone on to co-found I AM ALS and [indiscernible] After Care with my wife, who is speaking for me.

"Every patient you have heard from today, and nearly every respected doctor who actually treats ALS patients, recommends approval. Think about that for a second. Think about that. This community is crying out for help, not in 5 years, but now.

"I want you to imagine a world in which ALS patients live 20 years on average post-diagnosis instead of 2 to 5. Now stop imagining and remember that we have created that world for once rapidly fatal diseases like HIV, cancer, cystic fibrosis, and multiple sclerosis. We built those worlds not with silver-bullet drugs, but with drugs that are just like AMX0035, which slowed progression, and then slowed it even further when combined with other treatments.

"As a prior speaker mentioned, a 2017 JAMA oncology review found that of 62 cancer drugs

approved from 2003 to 2013, the average survival benefit was just 3 and a half months. That is how we transform a disease from fatal to chronic. We extend survival, drug by drug, bit by bit. Similar drugs are being approved for cancer. Why not for ALS?

"In preparation for today, I read every single word of the Amylyx and Aduhelm submissions. FDA's Aduhelm's submission has a humanity and urgency that is utterly, utterly lacking here. These are FDA's words then.

"Quote, 'FDA considers it critical to intervene in Alzheimer's disease and neurodegenerative diseases, in general, as early as possible given the complexity and possible irreversibility of pathophysiological deterioration responsible for clinical findings,' end quote.

"In contrast, when we have a small biotech here, with a small patient population here, whose trial actually hit primary endpoint, FDA chooses instead to focus on whether death equals survival and on knocking down the open-label extension,

which in fact they told the sponsors to undertake? Why do we not have urgency and humanity here?

"In the 2019 ALS guidance, FDA boldly declared, quote, 'When making regulatory decisions about drugs to treat ALS, FDA will consider patient tolerance for risk and the serious and life-threatening nature of the condition in the context of statutory requirements for safety and efficacy.' In contrast to this bold statement, FDA's actions and delays here have already meant that over 12,000 Americans have died without being able to try this safe drug.

"It is time to put an end to these broken promises. Applying the FDA's own guidance, this committee should recommend approval of AMX0035. In this 100-page back and forth between Amylyx and FDA, which I read very closely, there are agreements on two key things. First, that AMX is safe, and second, there is agreement that it slows progression. The only disagreement is in how much it slows progression.

"If you ask 10,000 ALS patients if they

would take a drug that is safe and may slow their progression by up to 25 percent and extend their life by as much as 6 and a half months, I guarantee you 10,000 out of 10,000 will say yes, and they'll deal with any minor potential side effects like diarrhea.

"Look, let me be super clear. A no vote by you could result in another 18,000 humans dying without access, and it will set back discovery in this rapid 100 percent fatal disease by years. Let me also be clear about this. Those who have spoken today against approval do not -- do not -- speak for this community, and they are not the sector's respected experts.

"Let me say this once again. Every patient you heard from and nearly every respected doctor who actually treats ALS patients recommends approval. This community is crying out for help, not in five years, but now. Please listen to the patients. Please listen to today's scientific and clinical ALS experts. Please, please, make the right choice."

DR. MONTINE: Thank you.

Speaker 25, your audio is now connected. You can begin by introducing yourself, stating your name and any organization you represent.

DR. SHAMASKIN: I'm Dr. Joel Shamaskin, and I represent no organization. I'm speaking from two perspectives, one as a retired primary care doctor and professor emeritus of medicine, and the other as a prison living with ALS. These experiences frame my thinking about the importance of AMX0035's approval.

Most primary care doctors recall all their patients with rare diseases like ALS, and I'm no exception. While each patient's course had its unique qualities, a common thread was woven through each. The decline they faced was painful to witness, and that every visit the message to them was the same. I had no good treatment to offer.

This experience informed how I reflect on my life with ALS and why I believe the new drug offers so much. Preservation of function means everything to us, and retention of two FRS points over

24 weeks is very significant. A 2-point loss over any time frame produces a major impact on social interaction. Patients like me who function at a 3 in most domains, by dropping a single point might move from being independent at meals to relying on someone to cut their food.

Loss of one speech domain point can make a person reluctant to participate or keep up with a fast conversation. These are the kinds of changes from which it's easy to see a patient heading down the road to isolation, loss of self-worth, and depression. Retaining two FRS points over 24 weeks may seem like a modest benefit, but in reality for people like us, it is very significant.

Thirty years ago, I cared for my first patient with AIDS and my first with ALS at the same time. They were alike in that they each survived under three years. However, over the subsequent three decades, the experiences of people with these two diseases cannot have been more dissimilar. During those years, we've thankfully gone from having one drug for HIV to 24, and we all know

where we are for ALS.

In conclusion, adding AMX0035 can be the first of many add-on drugs to get incremental extension on life span and add to that quality of life. A modest additional effect can make ALS more livable, and a very low risk-benefit ratio is a main reason to approve it now. Thank you.

DR. MONTINE: Thank you.

Speaker 26, your audio is now activated. Please introduce yourself, stating your name and any organization you represent.

DR. WOODS: Hi. I'm William G. Woods, MD. I represent myself, and I have no conflicts of interest.

I am an academic physician, specifically a pediatric oncologist, and a clinical researcher with extensive experience at the national and international level. I've served on NCI advisory committees which review and approve clinical trials such as the one being discussed today. I have ALS.

We have taken the cure rate of childhood cancer, in my 45 years of professional life, from

35 percent to 80 percent cure, and we mean cure. How? We did it with single randomized clinical trials not blinded, almost never two trials. The vast majority of drugs that we have used, including today, are not even FDA approved for use in kids. We cannot afford in kids to wait for confirmatory trials when the design is well done such as the AMX0035 trial.

Now, it is known that the Office of Neurosciences is, in fact, a very cautious institution. I know this because of friends that I have within the FDA. This was true for the Office of Cancer as well until Richard Pazdur took over as director, probably 10 years ago. He transformed that branch, and it was a good thing because about the same time, a ton of molecular inhibitors were coming down the pipe that required rapid testing and approval when necessary so that we could try more.

The use of secondary endpoints in small studies has been frequently used for new agents. We use the process of accelerated approval, which

I've not even heard talked about today among the neurosciences folks. But what this does is it allows the cancer side of things to approve drugs, and then require the drug company to follow patients subsequently treated very carefully, with subsequent review by the Center of Excellence in Oncology. If a drug does not show a particular indication in a particular cancer, it is stopped, and the license is withdrawn.

I do not understand why, in fact, you can't do the same thing in the Office of Neurosciences. It makes no sense to me, unless I'm missing something. We weigh risk and benefit. In this case, the risks are minimal and the benefits are huge. We could save -- as a lady, number 24, said -- something like 15 [000] to 20,000 lives in the three years it would take to finish the larger trial.

DR. MONTINE: Excuse me. I'm sorry to interrupt you, but you're considerably over your time, so if you would please wrap up your comments.

DR. WOODS: I will. The timer says that I

have 15 seconds left, but I will wind it up.

This study isn't imperfect -- most clinical trials aren't -- but I'm asking you to do the right thing for people with ALS.

DR. MONTINE: Thank you very much, and I apologize again for interrupting you.

I'd like to thank all of our speakers in the open session, especially the patients and their loved ones. It's extremely valuable input for the council and the committee.

We're now going to take a five-minute break.

MR. HENSON: Am I on? I'm sorry. My microphone came on. Sorry.

DR. MONTINE: No problem. So we're going to take a five-minute break, so we'll reconvene at let's say -- well, let's make it 7 minutes. We'll reconvene at 50 minutes past the hour, where we'll take up additional panel discussion and questions.

Okay. Thank you, everyone. We're at break.

(Pause.)

DR. SEO: Dr. Montine, I apologize. We do have one speaker, speaker 27.

DR. MONTINE: Oh.

DR. SEO: We'll be going to break after speaker 27.

DR. MONTINE: My apologies. I'm sorry, speaker number 27. I thought we were ending at 26. My apologies. Please proceed, introducing yourself and stating who you represent.

MR. HENSON: I very much appreciate it, and I will probably need substantially less than three minutes. My name is Mike Henson, and I represent a group called No More Excuses, and I have no financial disclosures, and I own no Amylyx stock.

Our 13,000 members would like to chime in briefly and say, please approve this drug. No drug is perfect, but I'd like to tell you just a brief story. In June of 2019, we were fortunate enough to sit across the table from Dr. Janet Woodcock and Dr. Peter Marks. At that meeting, I spoke for our group and told Dr. Woodcock that ALS could be, and should be, a treatable chronic disease.

That was almost three years ago now, here, and in a couple of months it will be three years.

Unfortunately, nothing has changed as far as patients in terms of approved drugs since that date. Imagine being on the Titanic that is sinking, and you get into a lifeboat, and somebody says, "You can't get in that lifeboat," or, "You better get out because it is not government certified yet."

That is literally the situation that we face today with ALS. We're not being allowed access to several drugs, in fact, and I think it's a real tragedy because this drug, AMX0035, while not perfect is certainly good enough to get into the lifeboat and to use as the first of many we hope to come.

I'll just close by saying that the general defeatism that we see in ALS must end. Last year in October, I AM ALS' president and co-founder, Bryan Wallach, gave an impassioned speech along with his wife at Congress, in the U.S. Congress. That speech, to me, represents exactly what we need to do in ALS today. We must begin to take chances -- and not risks, by the way -- just

chances on these types of drugs that meet their primary endpoint but that are not perfect.

At that meeting, the FDA promised to use regulatory flexibility. We haven't seen it yet. This could be the first. On behalf of our 13,000 members, I implore you to please approve this drug. Thank you.

DR. MONTINE: Thank you, and my apologies again for my confusion with the last speaker.

MR. HENSON: No worries. Thank you.

DR. MONTINE: Thank you to all our speakers.

As I said, we'll now break until 55 minutes past the hour, and then we'll reconvene with further panel discussion and questions. This closes the open hearing portion of the meeting, and we will no longer take comments or questions from the audience. Thank you. We'll reconvene at 3:55.

(Whereupon, at 3:47 p.m., a recess was taken.)

Clarifying Questions (continued)

DR. MONTINE: Welcome back, everyone. We'll now move to further panel discussion and questions.

I will orient people to time. We're about 20 minutes behind schedule. I apologize for that, but we felt it was important, especially for patients and their families, to have the opportunity to speak.

I have five individuals, groups, that have already asked to speak, so I'll go in order for those five, the group from Amylyx, then Drs. Traynor, Gould, Fischbeck, and Robert Alexander. And then after we go through these five, anyone else who wishes to speak will follow the same format as before of raising your hand, and I'll acknowledge you.

So I'll hand it over now. I'll please ask everyone to keep their comments focused and crisp. I'll hand it over to the team from Amylyx.

DR. TIMMONS: Thank you. This is Dr. Jamie Timmons from Amylyx. First, I appreciate the FDA providing the opportunity for us to correct a statement made earlier about the statistical analysis plans in CENTAUR.

To clarify, both the randomized-controlled

phase and open-label phase statistical analysis plans were finalized and submitted prior to randomized phase unblinding. They were not revised after unblinding.

Given that the mITT population was prespecified for the survival analyses but that ITT was the analysis that we also wanted to do, we submitted a supplemental statistical analysis plan in April 2020 that detailed the method for that ITT survival analysis. It does not supplant the original statistical analysis plan, which, again, was not changed after submission.

Next, I'd like to address two, after the break, questions that came up. The first, Dr. Hendrix will address the question from Dr. Follmann regarding the comparison of the randomized-controlled phase and open-label phase ALSFRS-R slopes.

DR. HENDRIX: Suzanne Hendrix. What you can see here is the slide that had the question with the confidence intervals added, and just to orient you, these are confidence intervals around each

point estimate.

When we look at the 1.24 at the top and look at that confidence interval around it, you want to look at the number underneath and see if it's included in that confidence interval to see if they're different from each other. What you can see is that in the first column, the 1.24 is different than the number below it, 1.66, and on the right-hand side you can see that the 1.26 is similar to and the confidence interval includes the 1.37, suggesting that the patient to have newly gone on to treatment from the placebo arm are getting a more similar slope to the participants who have been on active treatment from the first phase into the second phase as well.

Now, just to put that in context, I need to also show the participants who did not go into the open-label phase, and on this slide you can see those participants.

On the bottom here, we have the participants who are not going to be on the label. There are 33 in the original randomized active arm, 14 in the

original randomized placebo arm, close to the 2 to 1 randomization, suggesting that the participants that we're looking at are similarly balanced between the groups, the ones who participated, and then also the ones who didn't.

On the right-hand side here, you can also see the survival numbers, where the difference between 15.6 and 7.5 is about 8 months. An additional 8 months in the open-label phase resulted in an additional 8 months of survival, as seen in the right-hand column, the difference between 29 and 20.8. And on the bottom, an 2.7 months of exposure results in, again, about a 2-point additional survival for those who did not go into the open-label phase but had some early AMX treatment. Thank you.

DR. TIMMONS: This is Dr. Timmons again. Finally, to finish the question on neurofilament raised during our Q&A, prior to our break that we were not able to complete, here is Dr. Shefner.

DR. SHEFNER: Hi. Jeremy Shefner. I just want to make the point that neither neurofilament

light or heavy chains, known to be a treatment sensitive biomarker in ALS, there's been no ALS clinical trial in which there's been efficacy signal and a reduction in neurofilament.

There's one recent late-phase study in which neurofilament was reduced quite dramatically and statistically significantly. That study was not associated with the significant clinical signal with respect to efficacy. That's the body of knowledge about the treatment responsiveness for neurofilament.

DR. TIMMONS: Thank you. That concludes the Amylyx portion.

DR. MONTINE: Thank you. Thank you, all.

Next is Dr. Traynor.

DR. TRAYNOR: Hi. This is Bryan Traynor here. I have a question for Amylyx. I'd like to draw your attention to the rate of decline of the ALSFRS for the 48 patients in the placebo group. It's stated to be 1.66 per month, and I would like to ask your opinion as to whether this is what will be expected or whether it will be higher than

expected in a similar group of 48 patients that will be taken from an ALS population.

DR. TIMMONS: Thank you. This is Dr. Timmons. Based on the clinical modeling done with the specific inclusion criteria used in CENTAUR, we did anticipate this rate of progression for the placebo group. I'll have Dr. Paganoni comment further.

DR. PAGANONI: Hi. This is Sabrina Paganoni. Yes, that's exactly right. We spent quite a bit of time when we were designing the trial. With several colleagues, and Dr. Schoenfeld in particular, we analyzed prior clinical trial databases to select inclusion/exclusion criteria that would allow us to enroll a relatively homogeneous population that was predicted to progress at that rate, and that's exactly what we saw in the placebo arm.

DR. TRAYNOR: May I ask a follow-up question?

DR. MONTINE: Please.

DR. TRAYNOR: Dr. Paganoni, your eligibility

criteria would likely push the rate of decline -- because you're selecting patients who are earlier in the course of the disease and have a [indiscernible] capacity that's greater than a certain percentage, would you expect that rate of decline to be a little bit lower than what was observed in this study? I'm just puzzled because you say you've compared it to previous clinical trials, but 1.66 really does seem to be quite high.

DR. PAGANONI: That's a great point. The reason we were able to enroll a fast progressing population is because there was another key inclusion criteria, and that's the diagnosis of definite ALS by ALSFRS-Revised. So the disease was already diffused to 3 out of 4 body regions.

DR. TRAYNOR: Okay. Thank you.

DR. MONTINE: Thank you.

Dr. Gould, please?

DR. GOULD: Can you hear me ok?

DR. MONTINE: Yes, I can.

DR. GOULD: That's fine.

My question is to both parties. I'm trying

to understand a little bit more how both parties viewed the issue with edaravone use in the clinical trial. It seems at baseline there was a pretty substantial imbalance, and then during the comments of the trial, it appears there's a disproportionate amount or disproportionate number of subjects on the active that were then started on edaravone.

Maybe in the sense of addressing how serious that confounder is, the other question, these two molecules, or at least edaravone, is there a possibility -- is there a reason one would posit a pharmacodynamic interaction between AMX0035 and edaravone given its antioxidant or pre-radical scavenging and mitochondrial protecting qualities as well?

I'd like to hear that one, and then, would it be also possible to get a sense from either party, an effect size that is in the Cohen D or standardized mean difference? It's difficult to conceptualize this across other therapeutic areas to understand whether this is -- we know that 25 percent in the scale is already based on at

least one paper on the borderline of quite low, quite modest, but it'd be helpful to contextualize that treatment effect across other therapeutic areas when we have the standardized mean difference.

I'll stop with those two. Thank you.

DR. TIMMONS: Hello. This is Dr. Timmons. The Amylyx team is happy to address first since you asked for both parties.

In terms of the edaravone question, there was a baseline imbalance in the use of edaravone in the study with more placebo participants at baseline taking edaravone compared to the AMX0035 group, as seen in the darker blue portion of this graph. There were a small number of in-study initiations of edaravone. As seen, there were slightly more in the AMX0035 group compared to the placebo, 13 percent versus 4 percent.

We did prespecify sensitivity analyses to account for this difference, and I'll bring those up here. What I'll show here is the time-dependent sensitivity analysis, where we're adjusting for

time on edaravone and also riluzole during the randomized-controlled phase. When we perform this analysis, we see results very consistent with the primary outcome, indicating that the functional benefit is maintained even when we correct for that in-study use of edaravone and riluzole.

Our next question in terms of the potential interaction between AMX0035 and edaravone, the study was not designed to evaluate the efficacy of edaravone and riluzole. It's really designed to evaluate the impact of AMX0035 on top of standard of care of those two therapies. So we're really not able to comment on their relative efficacy, only that the effect that we see is independent of AMX0035. We do not, however, see any potential drug-drug interaction with edaravone and riluzole, if that was part of the question.

I'll ask Dr. Hendrix to answer the last part of the question in terms of the standardized mean difference.

DR. HENDRIX: Thank you. Dr. Hendrix again. The question was whether Cohen D might shed some

light on the type of effect that we're seeing here.

The 25 percent slowing is helpful of course to talk about how it relates to a degenerative disease, slowing it by 25 percent, but the Cohen D that we calculated for the prespecified primary endpoint, the same one that had the 0.034 significance, was 0.38. So that's between what people would normally consider a small or a moderate effect size. It's closer to the moderate side. So 0.38 is the Cohen for this study over the first six months.

DR. TIMMONS: Thank you for your answer.

DR. MONTINE: Thank you.

FDA team, would you care to comment?

DR. FREILICH: Hi, Dr. Traynor. This is Dr. Emily Freilich again. Thank you for that question. I'll just speak to the edaravone point again.

As we mentioned briefly earlier, I think the imbalance is there, and the impact of it is unclear. We noted that more patients on placebo were on concomitant medications at baseline, which,

as we indicated, could indicate a difference in their underlying disease and why they were on it at baseline or not, and then more patients on the AMX0035 arm initiated treatment with edaravone during this study.

While these are all small numbers, it's a small study, so a change in just a few patients could potentially have confounded the study results in terms of knowing if the slowing down of disease was due to the drug itself or to the combination of both drugs or the edaravone itself.

I don't know of any pharmacodynamic effect that would lead to an interaction. I don't know if anyone else on the FDA team wants to speak to that. I'll also let Dr. Massie speak to the question on standardized means.

Dr. Massie?

DR. MASSIE: This is Tristan Massie. I was wondering if I could speak on the edaravone use issue.

DR. MONTINE: Please.

DR. FREILICH: Go ahead.

DR. MASSIE: I think the difficulty is that it's a post-randomization covariate, so it may create an imbalance. The sponsor acknowledged in their open-label extension analysis plan that any model that corrects for a post-randomization covariate may interfere with the assessment of the treatment effect. The problem is it's a post-randomization event which can create an imbalance, so their model is not conclusive because it depends on strong and unverifiable assumptions.

DR. MONTINE: Thank you.

Any further comments with respect to Dr. Gould's questions?

(No response.)

DR. MONTINE: We'll move then.

Dr. Fischbeck, you're next.

DR. FISCHBECK: Sure. This is Dr. Fischbeck. I have a couple of questions related to the ALSFRS-R, I think mostly for Dr. Shefner, but also for others. One is with regard to the linearity of the ALSFRS-R that's often cited and shown in studies that include a

large number of patients that the average decline is down.

There's a recent publication of the results of the Answer ALS study that had about a thousand patients. They showed a spaghetti plot of the ALSFRS results that showed patients were all over the place in terms of some going down rapidly, some more slowly, some going down and then up, and others going up and then down. I wonder how that goes together with what's been said about linearity. That's the first question.

DR. SHEFNER: Hi. This is Jeremy Shefner. The ALSFRS-R is an ordinal scale of, and there's no absolute reason why it has to decline really early. But it is the experience in clinical trials, on the order of 6 to 12 months, that the ALSFRS is a scale that can cause linear layover, over groups.

You can see from --

DR. TIMMONS: It may not come up.

DR. SHEFNER: Oh, it may not come up.

But from all recent trials, the deviation from linearity is not significant. You're right;

the ALSFRS data shows some non-linearities, but those data are acquired over the course of approximately 5 years, not the 6-month to 12-month period that that clinical trial was conducted for.

DR. FISCHBECK: Yes, that's a good point. It was also collected a different way from the clinical trial here.

The other question I had is about the MCID, the minimum clinically important difference of a change in the ALSFRS-R. I wonder where that comes from or what data there is to support it. The published paper said that there isn't a clear signal from the literature.

What I was able to find was a paper from NEALS back about 12 years ago that sought expert opinion. There were over 40 respondents, and it looked quite scattered. A 20 percent change was considered to be somewhat meaningful, and to get up to meaningful or very meaningful, you had to get at least 25 percent or more change. That's from the experts, NEALS study investigators.

I wonder if there's ever been a good study

of how patients feel about change or what the minimum detectable change by the patient population is that's participating, whether that's ever been done in NEALS or elsewhere, or whether it could be incorporated. It seems pretty easy to incorporate in a clinical trial by just asking patients whether they noticed a change, and see how it correlates with the change in the ALSFRS-R.

DR. SHEFNER: This is Jeremy Shefner. Thanks for that question, which is an incredibly important one. You've correctly identified the one paper that I know about that really addresses this issue. It's an expert witness testimony from investigators, not patients.

I think that at 25 percent or more, virtually all investigators rated that effect as moderately to greatly clinically significant, but that's a limited data set. There is an effort underway now to really rigorously establish a minimally important difference for the ALSFRS, but that's just in its infancy. We don't have data right now.

DR. FISCHBECK: Thank you.

DR. MONTINE: If I may, Dr. Fischbeck, I'll circle back if you have additional questions. I just want to be sure everyone gets a chance, if that's ok.

DR. FISCHBECK: Yes, at first time.

DR. MONTINE: Great. Thank you.

Dr. Robert Alexander, you're next.

DR. R. ALEXANDER: Yes. Hi, Dr. Montine. It's Robert Alexander. I don't have any further questions or comments.

DR. MONTINE: Oh. Thank you.

Dr. Nath, you're next.

(No response.)

DR. MONTINE: Dr. Nath, you may be on mute.

DR. NATH: Yes. Sorry. It took me a little bit to unmute myself.

My question is in regard to the feasibility of a placebo-controlled study. This is directed towards Amylyx. The concern is that during the comment section, we heard that Turso is available over the internet easily, and I understand that

sodium phenylbutyrate is also available, although it is quite more expensive. But if these things are easily available to people -- and it doesn't really matter whether in Europe or in the United States -- I wonder how a placebo-controlled study would still be feasible. If somebody could clarify that for me, that would be great.

DR. TIMMONS: This is Dr. Timmons. The exclusion criteria for the PHOENIX study specifically do exclude the use of sodium phenylbutyrate or taurursodiol in the study.

DR. NATH: No, that I understand. But my concern is that if people can just get it, why would they enroll in a study when you have a chance you could end up on placebo? You can just get it over the internet. That's a problem in any placebo-controlled study. If a drug is easily available and they can just obtain it, then they won't enroll in a placebo-controlled study.

DR. TIMMONS: Understood. In terms of Tudca, taurursodiol, one thing to clarify is that the specific pharmaceutical grade of taurursodiol

that's used in AMX0035 is not available on the internet or on Amazon, and the Tudca that is available for purchase may not actually be Tudca. It's an unregulated supplement.

DR. NATH: What about the phenylbutyrate?

DR. TIMMONS: Phenylbutyrate of course would require a prescription and an off-label use. In terms of the way ALS clinical trials are performed, I can ask Dr. Paganoni to comment on how these supplements and off-label uses are controlled in terms of clinical trial enrollment.

DR. PAGANONI: Yes. This is Dr. Paganoni. In terms of the phenylbutyrate, Dr. Timmons is correct; that's available by prescription. The cost is exorbitant. So again, I don't think that's readily available for the vast majority of patients, and I assume the same would be true in Europe in terms of Turso, as already discussed. It's an unregulated product.

I think as an investigator, we always have that discussion with our patients, and that's what I do. Even when I enroll, right now, patients in

other clinical trials, I ask them, "Are you using supplements or products that you purchase online that will be exclusionary during this trial?" And patients do tell us, and they make decisions. I have some patients who tell me I'd rather take the cocktail of supplements I find online and don't enroll in trials, and others that understand that enrollment in trials is also important for the community.

So the same applies, I guess, across the entire industry. Patients have to make that choice, if they want to enroll or not in a clinical trial.

DR. NATH: Thank you.

DR. MONTINE: Thank you both.

Mr. Weston, you're next.

MR. WESTON: Yes. Thank you.

I'm not sure who this question is directed to, one of the Amylyx folks, and I'll let you guys fight it out, if I can articulate my question.

It's well-known there are a large number of persons living with ALS who outlived the frequently

stated 3 to 5 years of expected survival. This population as a general rule does not qualify for any clinical drug trials, but there may be a few exceptions. The CENTAUR study, everybody knows, included only persons who had symptom onset within 18 months.

In plain English -- remember, I'm the patient representative, not a statistician -- can you describe the likely impact on ALSFRS scores for those who have had ALS for more than just a few months? I'll just leave it open-ended like that. Thank you.

DR. TIMMONS: Thank you. This is Jamie Timmons from Amylyx. Given the proposed mechanism of action, the way that AMX0035 is proposed to work, which is on the pathways that lead to the neuron to die, we would propose that this therapy could be applied to all people with ALS.

Of course, it's important to remember that we've only studied specifically in the CENTAUR population, so the PHOENIX clinical trial, we'll provide additional data and additional real-world

studies, and we'll also provide additional data there as well, too.

I'm going to have Dr. Shefner comment as well, too, from his standpoint as a clinician.

DR. SHEFNER: Hi. This is Jeremy Shefner again. I want to comment just based on the edaravone development program and the Amylyx development program, in which inclusion criteria were established to create a population that was relatively homogeneous and progressed at a predicted rate.

This isn't a phenotypic distinction, so there's no assumption on the part of the investigators, or I think the general community, that this is a group of ALS patients that is ideologically or pathophysiological distinct from those who are more slowly progressive. So the hypothesis would be that if there's a signal in this group that's chosen to be able to see this effect, we would expect that that same effect would apply to others that don't meet those criteria. It's a theoretical argument, it's not a fact-based

argument, but I think it's a reasonable one to make.

DR. MONTINE: Thank you.

Dr. Follmann, you're up next.

DR. FOLLMANN: Yes. Thanks. This is Dean Follmann. I have two questions. One is for Amylyx. It regards to the survival endpoint. I know the FDA mentioned that they thought you were perhaps elevating the importance of the survival endpoint, and I'd just like to hear your response to that.

DR. TIMMONS: This is Dr. Timmons from Amylyx. In terms of the prespecified hierarchy for long-term follow-up -- I can pull that up here -- the composite survival endpoint of that includes overall survival, hospitalization, and tracheostomy. Permanent assisted ventilation was secondary in the hierarchy. This is prespecified, and the statistical analysis plan was signed off on before randomized-controlled phase unblinding.

This hierarchy never changed. This composite survival endpoint has always been second

and was never elevated. Perhaps where the confusion may come in is the specific ITT overall survival supplemental statistical analysis plan, which is really put together just purely to detail those methods for the ITT overall survival analysis. But again, that composite analysis, which includes the individual overall survival outcome, was never elevated and was prespecified.

DR. FOLLMANN: Could you go back to that previous slide? You have a hierarchy of endpoints. So was the convention that you first test the first one, the ALSFRS-R, for long-term follow-up, and then if that's significant, go on to the next one?

DR. TIMMONS: I'm very sorry. This is Dr. Timmons. I couldn't quite hear what the question was there.

DR. FOLLMANN: Well, there's a proposed hierarchy here, so does that mean that you would first test rate of decline, and if significant, go on to the next one?

DR. TIMMONS: That is correct. The ALSFRS-R rate of decline in the long-term follow-up did

reach statistical significance, then this composite survival endpoint was next.

DR. FOLLMANN: Thank you.

My other question has to do with the FDA. I guess, Dr. Freilich, I'm just interested in a little more context about this one study. Was the expectation, when you had initial discussions that this might form the basis for approval if it was substantial evidence -- how was this study thought when you were discussing with the sponsor initially?

DR. FREILICH: Thank you. This is Dr. Freilich. I think that you mean initially when they first came to us with the study, which was this was a phase 2 study, but we definitely understood that if it appeared to be an adequate and well-controlled study, that it could contribute to the contribution of determination of efficacy.

I think once we had seen the top-line results, we initially raised the concern about the ability of the study to stand on its own as a single study, and that's why we started talking to

them about the need for a second study. Again, as we've mentioned earlier, we then thought that the survival endpoint did warrant a more critical consideration of the data, and that was why we had them submit for the NDA.

DR. MONTINE: Thank you.

We're running short on time. I appreciate the terrific discussion that we're having. We have three more committee members that wish to ask a question, so it will be just those three, and then I'm going to have to call time, so please keep your questions and answers as concise as you can.

Drs. Caleb Alexander, Fischbeck, and then Gould. Dr. Caleb Alexander, you're your next, please.

DR. C. ALEXANDER: Hi. This is Caleb Alexander. I had a question. I'm still trying to get my head around the really favorable open-label, post hoc analyses that examined death alone. I understand the concerns and qualifications about these, but I'm trying to reconcile them a bit with the results of the randomized 24-week trial that

didn't show favorable outcomes for the composite.

I know that the FDA has commented that there was an absence of correlation between exposure and survival in this open-label analysis, so understanding the other concerns that would exist regarding this analysis as well, I just was wondering if either the sponsor or the FDA could provide any additional information that examines survival as a function of drug exposure.

DR. TIMMONS: This is Dr. Simmons from Amylyx. I'm happy to begin.

Here we're seeing all participants that were randomized in CENTAUR, and I believe that the analysis that the FDA performed excluded about 70 or 75 percent of participants to come to that conclusion. When we look at all participants, we do see that longer exposure to AMX0035 was associated with longer survival in this subgroup analysis.

Of course, these are subgroups, so we have to look at this without lens, but looking at the participants that were enrolled in the open-label

phase -- AMX0035 group on the top, placebo on the bottom -- we see that those participants that had the longest exposure to AMX0035 did have the longest median survival, and then that carries through down the line to those participants that did not enroll in the open-label phase as well.

Dr. Hendrix has one additional thing to add.

DR. HENDRIX: Just to remind you, then, on this plot, what we're looking at is the group separated into those who enrolled and did not enroll in the open label. When we do the full analysis with all 136 participants followed to the end and 137 censored at the last time we observed them, we're actually observing a weighted average of the 15.6 months of exposure in the active arm here with the participants who did not enroll and only had 2.7 months exposure, and then the placebo arm is actually those participants with 7.5 points exposure averaged with the participants with no exposure.

So the overall survival analysis is essentially a lower bound, what we would have been

able to observe if we had a placebo group all the way to the end.

DR. C. ALEXANDER: Thank you. And if you can just leave this slide up, if the FDA wanted to comment on either the top two rows of this slide or just the general matter of whether or not there was a correlation between exposure and survival, please.

DR. FREILICH: Hi. This is Dr. Freilich. I think, one, we tried to do a correlation between exposure and survival and could not find that they correlated together due to the number of dropouts and discontinuations.

I think one of the things to keep in mind with this, what is currently displayed on the screen, is that a lot of the patients did discontinue due to ALS progression, so it does make sense that survival was longer in patients who did stay in the study longer. However, when we looked at individual patients and the duration of time they actually took the drug, we did not see an exposure response curve developed.

DR. C. ALEXANDER: Thank you.

DR. MONTINE: Thank you both.

Dr. Fischbeck, if you could please ask your remaining question.

DR. FISCHBECK: We don't need to spend a lot of time on this, but I'm curious. This would be a question I guess for Justin Klee or maybe Joshua Cohen about the rationale behind choosing these particular drugs to put together in AMX0035 when there are other more potent and selective drugs available that hit the targets that you had in mind.

I'm speaking particularly about phenylbutyrate when there are much more -- thousands sometimes more -- potent and more selective ACE [indiscernible] inhibitors that could have an effect on ER stress.

DR. TIMMONS: Justin Klee will take this one.

MR. KLEE: This is Justin Klee. I would say that one of the challenges I think we all face in neurodegeneration is how do we bridge that

translational gap? I think the way that we tried to approach this is to look at one of the main reasons we know that neurodegenerative diseases occur -- maybe the fundamental reason -- which is the nervous system degenerates and the neurons die. So we sought to look in preclinical models of a variety of different insults that would cause neuronal death that may then help us translate into a clinical effect, not just a preclinical one.

In our experiments, we were looking at the effects of ER stress and mitochondrial dysfunction in a variety of different cell-death models, and what we found is that both of these individual drugs are quite effective, and not just in our hands, but in many other labs they found the same thing.

What we found in our studies as well is that the combination was considerably more efficacious than just using either component alone, so it was on that basis that we then decided to go forward and bridge that translational gap to see if this would actually be a clinical effect and not just a

preclinical one.

DR. FISCHBECK: Thank you.

DR. MONTINE: Thank you both.

Dr. Gould?

DR. GOULD: Yes, a quick question to the Amylyx folks. You have that confirmatory study up and running, and you guys stated that you have the vast majority of subjects in Europe. I'm just trying to understand. In the universe where 0035 is approved in the U.S., what is your predicted impact on the power of the ongoing study? Are there ways of accelerating and/or expediting the delivery of the results from the ongoing study?

DR. TIMMONS: This is Dr. Simmons from Amylyx. The PHOENIX study is well powered. Even if the planned 200 participants in the United States are not able to complete the study, it is currently powered at 95 percent for the primary endpoint.

DR. MONTINE: Thank you.

Dr. Apostolova, you're the last one up.

DR. APOSTOLOVA: Okay. Can you guys hear

me?

DR. MONTINE: I can.

DR. APOSTOLOVA: Good.

Just to clarify, you just presented some additional survival analysis. Did these just include deaths or also included tracheostomies, a permanent ventilator, and hospitalizations, if I'm not mistaken?

DR. TIMMONS: This is Dr. Timmons from Amylyx. To clarify, are you asking about the subgroup analysis that was shown?

DR. APOSTOLOVA: Just now, yes, the last two slides.

DR. TIMMONS: That analysis is deaths only.

DR. APOSTOLOVA: Thank you.

Questions to the Committee and Discussion

DR. MONTINE: Thank you all.

The committee will now turn its attention to address the task at hand, the careful consideration of the data before the committee, as well as the public comments.

We will now proceed with the question to the

committee and panel vote. I would like to remind public observers that while this meeting is open for public observation, public attendees may not participate, except at the specific request of the panel. After I read the question, we will pause for any comments or questions concerning its wording, then we will open the question to the panel. Dr. Jessica Seo will provide the instructions for voting.

Jessica?

DR. SEO: Thank you, Dr. Montine.

Question 1 is a voting question. Voting members will use the Adobe Connect platform to submit their votes for this meeting. After the chairperson has read the voting question into the record and all questions and discussion regarding the wording of the vote question are complete, the chairperson will announce that voting will begin.

If you are a voting member, you will be moved to a breakout room. A new display will appear where you can submit your vote. It will be no discussion in the breakout room. You should

select the radio button that is the round circular button that corresponds to your vote, either yes, no, or abstain. You should not leave the "no vote" choice selected. Please note that you do not need to submit or send your vote. Again, you need only to select the radio button that corresponds to your vote.

You will have the opportunity to change your vote until the vote is announced as close. Once all voting members have selected their vote, I will announce that the vote is closed. Next, the vote results will be displayed on the screen. I will read the vote results from the screen into the record. Thereafter, the chairperson will go down the roster, and each voting member will state their name and their vote into the record. You can also state the reason why you voted as you did, if you want, however, you should also address any subparts of the voting question, if any.

Are there any questions about the voting process before we begin?

(No response.)

DR. MONTINE: I will now read the question.

Question 1. 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 or ALS?

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.

Are there any questions or concerns about the wording of this question?

(No response.)

DR. MONTINE: If there are none, then we will now begin the voting on question 1.

DR. SEO: We will now move voting members to the voting breakout room to vote only. There will be no discussion in the voting breakout room.

(Voting.)

DR. SEO: The voting has closed and is now

complete. Once the vote results display, I will read the vote results into the record.

(Pause.)

DR. SEO: The vote results are displayed, and I will read the vote totals into the record. The chairperson will go down the list and each voting member will state their name and their vote into the record. You can also state the reason why you voted as you did, if you want to, however, you should also address any subparts of the voting question, if any.

There were 4 yeses, 6 noes, and zero abstentions.

(Pause.)

DR. SEO: Dr. Montine, you may be muted.

DR. MONTINE: Yes. Thank you. I got double-muted somehow. Thank you, Dr. Seo.

We will now go down the list and have everyone who voted state their name and vote into the record. You may also provide justification of your vote if you wish.

We'll start with Dr. Nath.

DR. NATH: This is Avi Nath. I voted yes. I have to admit this was a very difficult decision for me, and I could have gone either way. But after weighing all the factors and facts presented, I touched over to the yes side.

DR. MONTINE: Thank you.

Dr. Traynor?

(No response.)

DR. MONTINE: Dr. Traynor, you may be muted.

DR. TRAYNOR: Sorry. I was double-muted indeed.

This is Bryan Traynor. This was also a difficult vote and decision. I voted no. I will state my four reasons for doing so. I thought that there was considerable concerns voiced by the FDA about the trial conduct and the interpretation of the results. I thought that the fact that the larger trial is underway that will provide the answers makes this an important point.

I felt that the rate of the ALSFRS decline observed in the placebo group seems to be on the high side. That's a personal opinion. And I think

that all of these things combined together indicate that, really, the applicant hasn't provided robust evidence required for approval on a single trial as outlined in 505(b).

DR. MONTINE: Thank you.

Dr. Jones?

DR. JONES: Yes. This is Dr. Dawndra Jones. I voted yes. I have to say this was a very difficult decision, but I felt like it was the right thing, and being the consumer rep, I really wanted to make sure that the consumer voice was really heard.

DR. MONTINE: Thank you.

Dr. Follmann?

DR. FOLLMANN: Yes. This is Dean Follmann. I voted yes. I also found this a very difficult decision, and I went back and forth during the day actually, but ultimately I agreed with the sponsor's primary analysis. I think a lot of the issues the FDA raised, I could understand it, but I think the arguments the sponsor made for using the shared baseline linear random effects model

resonated more with me.

I think this is a situation where we don't have a lot of death endpoints, so I think this is like a more efficient and appropriate way to look at the data. I wasn't concerned about the linearity so much or the imbalance of baseline variables.

Just to make two more points, somehow I thought establish a conclusion was not quite the bar as substantial evidence. ALS is a rare disease. These also entered into my mind. I would also say the survival analysis, where you were able to determine vital status on, I think, 136 of 137, to me did support the mixed effects model analyses. So all in all, this is the way I voted. It was difficult, but I did vote yes. Thank you.

DR. MONTINE: Thank you.

Dr. Caleb Alexander?

DR. C. ALEXANDER: Yes. Caleb Alexander. I voted no. I do want to first thank the sponsor, and trial participants and their loved ones, as well as the public speakers and FDA for making

today possible, and working so tirelessly to develop new treatments for what I know is a devastating disease.

It's clear that there's a very compelling degree of unmet need, and it's also clear that many with ALS would accept the product as is and are willing to assume the risks associated with it, including the risk that it may not work. As a husband and father of three young children, I don't have any doubt about the value of another day of life, let alone another month of life or more to be with the ones that you love.

But despite this, this law, and statute, and regulatory guidance are clear and, unfortunately, there are many features of CENTAUR that limit its persuasiveness as a stand-alone trial in a regulatory sense; in other words its persuasiveness in a regulatory sense. Those include its small size, baseline imbalances; even if you accept the method of modeling outcomes and the baseline model being appropriate, the treatment of missing data, the modest impact on the primary outcome, and the

absence of any statistically significant effect on secondary outcomes.

The open-label study has even more serious limitations for it to be used as supplemental and confirmatory evidence in this setting, including the absence of a control group; high rates of non-participation and dropout that we heard about; treatment of tracheostomy or hospitalization as death equivalents and a composite outcome; and post hoc analyses that examined death alone.

I hope that the PHOENIX study will provide -- I believe that it will provide very important information about this product under consideration today, and I hope that the protocol and the trial can be finalized expeditiously to the mutual satisfaction of both the applicant and FDA so as to avoid some of the matters that have arisen thus far in the course of this product's development. Thank you again.

DR. MONTINE: Thank you.

Dr. Fischbeck?

DR. FISCHBECK: Yes. I agree, and I, too,

wanted to say something to acknowledge the really moving testimony from patients and from patient organizations we heard during the open session. I, too, have taken care of ALS patients, and really have friends who are patients with ALS. There's no question, the burdensome nature of the disease and the huge unmet need for safe and effective treatment.

On the other hand, in terms of establishing the conclusion that it's effective, we were asked to look for substantial evidence with persuasiveness and robustness, and I think this one trial doesn't quite meet that bar. It was a problematic study, problems with the randomization and blinding, and all the other problems that Dr. Alexander mentioned that came up during the course of the meeting today.

I do think it would be a disservice to the patients and their families to move ahead and approve a treatment that is an uncertain benefit. It gets in the way of developing truly a safe and effective treatment if it turns out not to be

effective in phase 3. I hope that the phase 3 PHOENIX study is successful, but I think it's necessary to decide to move forward and approve this drug.

DR. MONTINE: Thank you.

Dr. Apostolova?

DR. SEO: Dr. Montine, I apologize for interrupting.

Dr. Fischbeck, would you mind repeating your vote into the record and stating your name?

DR. FISCHBECK: Yes. I voted no, and this is Kenneth Fischbeck.

DR. SEO: Thank you.

DR. MONTINE: Thank you.

Dr. Apostolova, please?

DR. APOSTOLOVA: Yes. This is Liana Apostolova, and regrettably I also had to vote no based on the preponderance of the scientific evidence we reviewed today. I, too, have friends with ALS, and it's a terrible disease. Just like Alzheimer's, there is no cure for these disorders, and they affect not only the patient but the whole

family, and it's really devastating.

I recognize that this is an unmet need and really important, but also considering the data, -- the unfortunate, or fortunate circumstance that there is another newly approved FDA treatment which provides survival benefit, but unfortunate for the trial that happened during the conduct of this trial during the enrollment phase, and the uncertainty of how that affects the clinical outcome, and the uncertainty of patients who might have dropped out from the active drug could have started edaravone, and that could have helped their outcome, and they were kept in the mITT analysis.

All of these concerns -- and with the statistical analysis from the FDA that was raised -- made me vote no today. The good silver lining is you have a trial ongoing that could potentially resolve the uncertainties that this trial presents. It's just the data isn't as strong as we would hope it would be.

DR. MONTINE: Thank you.

Mr. Weston?

MR. WESTON: Yes. Thank you.

First, to confirm that I voted yes on this question, for me it was not a particularly enigmatic or difficult choice, and I'll explain why.

I want to acknowledge, first, as a patient representative on this committee I expect to be compensated by the FDA in connection with preparation for and participation in this meeting; that's part of the gig. However, I want to also stress that I do not believe this expectation of being paid affected by independence or my objectivity and my analysis in my role as a patient representative.

I'm one of these folks that find humor in everything, including a neurodegenerative fatal disease, and I want to remind everybody I have ALS. I've had symptoms almost four years, so I'm quickly becoming an outlier, perhaps; maybe not. I'm not sure I trust all the numbers that are out there.

I'm going to resist quoting Mark Twain and his commentary about statistics -- I think

everybody knows that quote -- but I will inject some humor that comes from my brother's experience with some neurologists. He's always observed that neurologists can tell you what's wrong, but they can't do anything about it.

I think today we have an opportunity to forward a recommendation to the larger FDA that may help change this. Both the applicant and the FDA agree that this drug causes no material harm to people that take it. It further appears there will be no real negative impact on the currently enrolling PHOENIX phase 3 study, as best I understand what's being said.

Notwithstanding the training, and the certification, and the administration of the ALSFRS-Revised, it's a very subjective instrument. I've administered it to myself numerous times. I've had it administered numerous times, and it's not great, but for now it's the accepted measure until we get something better.

There are little arguments as to the major conclusions of the CENTAUR study, but the ALSFRS

shows a slower decline in function, and there's a somewhat longer survival period of somewhere around 5 years, maybe less, maybe more. Before I got ALS, I would have pooh-poohed that and said, "But what's death?" But as many of my fellow patients testified today, that can be a very big deal, particularly if your functional abilities are not declining rapidly.

I do think this is a case where the FDA should exhibit regulatory flexibility, notwithstanding the imperfection of the study and, by the way, the imperfection of their critique of the study. In my view, it is preferable that this drug be approved and made available nationwide rather than having desperate persons scrambling to combine its two ingredients and self-medicate.

We already have two marginally effective treatments, edaravone, which has been around for what? About five years; very difficult to use. And of course riluzole, which is easy to use but also marginally effective. I think we should add a third standard of care, or maybe a second standard

of care to the pharmacy.

Those of us that live with ALS often have a very, very high tolerance of risk, and those people should be allowed to decide for themselves. I don't know whether or how quickly insurance companies will begin to add this drug if it's approved to their formularies, but today the ingredients, if purchased on the open market, have to be paid for by individual patients, and at least one of these ingredients is damn expensive, as I understand it.

I, too, look forward to more and stronger data. I've never seen a study that doesn't recommend further study, so we need more data. We need more objective data both from the clinical study, as well as from use by non-study participants who are living with ALS that are able to take this drug, hopefully following its rapid approval. Thank you, Mr. Chairman.

DR. MONTINE: Thank you.

Dr. Robert Alexander?

DR. R. ALEXANDER: Yes. This is Robert

Alexander, and I voted no. I listened very carefully to the powerful testimony of the many patients who suffer from ALS and their family members, and I found it very moving. But in the end, I had to agree with FDA that the study on its own doesn't establish that this drug is effective in the treatment of ALS for the reasons they enumerated, including the relatively small initial sample size, and particularly the size of the placebo group; the amount of missing data; potential imbalances between the treatment groups; and probably more importantly, the modest effect on the primary endpoint and the weaker absent support from the secondary endpoints.

It was difficult to know how much weight to assign the survival analysis given the exploratory nature. So I think we really need to wait for the results of the confirmatory trial to determine whether or not AMX0035 is effective. Thank you.

DR. MONTINE: Thank you.

For the record, my name is Thomas Montine, and I voted no. Like my other committee members, I

wish to acknowledge the deep respect that I have for family members and loved ones of people with ALS and the deeply compelling testimonies that we heard today. I'm encouraged by the safety and encouraging data, promising data in CENTAUR for possible effectiveness of this drug combination, but on balance I thought that the data presented did not meet the threshold of being a single very persuasive study. As many others have said, I look forward to a rapid and successful conclusion, I hope, of the PHOENIX study. Thank you.

Before we adjourn, are there any last comments from the FDA?

DR. DUNN: This is Billy Dunn. I just wanted to say thank you, first, to the patients and all participants in our open public hearing who shared with us your perspectives. I echo the comments of, it seems, every committee member in responding to and acknowledging the strength and importance of those comments.

We stressed in our background materials the engagement that we've had with the community over

the years. That's very important to us, and it was represented today in the important input that you provided. I'd like to thank the committee members for their clearly scientific and dispassionate consideration of the information presented to them in the face of a very difficult data package. We hear your thoughtful analysis of the same issues that the sponsor and we have been discussing, obviously, for quite some time and working hard to consider.

We're deeply appreciative for your input. As we said at the opening, and Dr. Buracchio pointed out in her introductory comments, we sought and need your input into this decision, and we value it greatly, so we're deeply appreciative of your time and efforts in this regard.

Thank you, Dr. Montine.

Adjournment

DR. MONTINE: Thank you, Dr. Dunn.

With that, I will just briefly add my gratitude to everyone's time and thoughtfulness today: patients, their loved ones, patient

advocates, the team from Amylyx for their commitment to developing new therapies for patients with ALS, and then of course to the FDA staff for the tremendous amount of work they've done to evaluate this proposal and the team that put together a seamless meeting for us today.

So thank you all. We will now adjourn this meeting.

(Whereupon, at 5:03 p.m., the meeting was adjourned.)