FOOD AND DRUG ADMINISTRATION

CENTER FOR DRUG EVALUATION AND RESEARCH

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

Virtual Meeting

Wednesday, September 7, 2022

12:00 p.m. to 6:41 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

ADVISORY COMMITTEE MEMBERS (Voting)

G. Caleb Alexander, MD, MS

Professor of Epidemiology and Medicine

Johns Hopkins Bloomberg School of

Public Health

Center for Drug Safety and Effectiveness

Baltimore, Maryland

Robert C. Alexander, MD

Chief Scientific Officer

Alzheimer's Prevention Initiative

Banner Alzheimer's Institute

Research Professor, Department of Psychiatry

University of Arizona College of

Medicine - Phoenix

Phoenix, Arizona

Liana G. Apostolova, MD, MSc, FAAN

Distinguished Professor in Neurology

Barbara and Peer Baekgaard Chair in

Alzheimer's Disease Research

Professor in Radiology and Medical and

Molecular Genetics

Indiana University School of Medicine

Indiana Alzheimer's Disease Center

Indianapolis, Indiana

Thomas J. Montine, MD, PhD

(Chairperson)

Chair, Department of Pathology

Stanford Medicine Endowed Professor

Stanford University School of Medicine

Stanford, California

ACTING INDUSTRY REPRESENTATIVE TO THE COMMITTEE

(Non-Voting)

Jeffrey M. Dayno, MD

(Acting Industry Representative)

Executive Vice President & Chief Medical Officer

Harmony Biosciences

Plymouth Meeting, Pennsylvania

TEMPORARY MEMBERS (Voting)

Kenneth Fischbeck, MD

NIH Distinguished Investigator

National Institute of Neurological Disorders and

Stroke, National Institutes of Health (NIH)

Bethesda, Maryland

Dean Follmann, PhD
Assistant Director for Biostatistics
National Institute of Allergy and
Infectious Diseases
National Institutes of Health
Bethesda, Maryland

Avindra Nath, MD
Clinical Director
National Institute of Neurological Disorders and
Stroke, National Institutes of Health
Bethesda, Maryland

Bryan J. Traynor, MD, PhD
Senior Investigator
National Institute for Ageing
National Institutes of Health
Bethesda, Maryland

Mark Weston

(Patient Representative)

Person with Amyotrophic Lateral Sclerosis (ALS)

Lakewood, Colorado

FDA PARTICIPANTS (Non-Voting)

Billy Dunn, MD

Director

Office of Neuroscience (ON)

Office of New Drugs (OND), CDER, FDA

Teresa Buracchio, MD

Director

Division of Neurology 1

ON, OND, CDER, FDA

Emily Freilich, MD

Cross Discipline Team Leader

Division of Neurology 1

ON, OND, CDER, FDA

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

(12:00 p.m.)

Call to Order

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

My name is Thomas Montine, and I'll be chairing this meeting. I will now call the September 7, 2022 Peripheral and Central Nervous Drugs Advisory Committee meeting to order. Dr. Jessica Seo is the designated federal official for this meeting and will begin with introductions.

Introduction of Committee

DR. SEO: Good afternoon. My name is Jessica Seo, and I'm the designated federal officer for this meeting. When I call your name, please introduce yourself by stating your name and your affiliation.

We'll begin with Dr. Caleb Alexander.

(No response.)

DR. SEO: Dr. Caleb Alexander --

DR. C. ALEXANDER: Hi. Can you hear me?

DR. SEO: Yes, we can hear you, sir.

DR. C. ALEXANDER: Hi. Can you hear me?

DR. SEO: Yes. Dr. Alexander --

DR. C. ALEXANDER: Thank you

Good afternoon. Sure. My name is Caleb Alexander. I'm a practicing general internist and professor of epidemiology and medicine at the Johns Hopkins Bloomberg School of Public Health. Thank you.

DR. SEO: Thank you, sir.

Next, we have Dr. Robert Alexander.

DR. R. ALEXANDER: Hi. It's Robert Alexander. I'm a chief scientific officer at the Banner Alzheimer's Institute, and a research professor at the University of Arizona School of Medicine in Phoenix. Thank you.

DR. SEO: Thank you.

Dr. Apostolova?

DR. APOSTOLOVA: Yes. I'm Liana Apostolova.

I'm professor of neurology from Indiana University School of Medicine.

DR. SEO: Thank you.

Dr. Montine?

DR. MONTINE: Thank you, Dr. Seo.

Good afternoon, everyone. My name is Tom Montine. I'm professor and chair of the Department of Pathology at Stanford University.

DR. SEO: Thank you, sir.

Next, we'll go to our temporary voting members, and we'll begin with Dr. Fischbeck.

DR. FISCHBECK: Hi. This is Kenneth Fischbeck. I'm a neurologist in the neurogenetics branch of Intramural NINDS at the NIH in Bethesda.

DR. SEO: Thank you, Dr. Fischbeck.

Next, we have Dr. Follmann.

DR. FOLLMANN: Yes. Good afternoon. This is Dean Follmann. I'm head of biostatistics at the National Institute of Allergy and Infectious Diseases.

DR. SEO: Thank you, sir.

Dr. Nath?

DR. NATH: Yes. I'm a neurologist and the clinical director at the National Institute of Neurological Disorders and Stroke at NIH.

DR. SEO: Thank you.

Dr. Traynor?

DR. TRAYNOR: Hi. My name is Dr. Bryan Traynor. I'm a neurologist and senior investigator at the NIH, with expertise in ALS and other neuromuscular diseases.

DR. SEO: Thank you, sir.

And Mr. Weston?

MR. WESTON: Good morning, everybody. My name is Mark Weston. I am the patient representative on today's advisory committee, diagnosed with ALS three years ago next month and obviously still kicking, unlike some of my friends, three of whom I want to mention.

April 1st, Bridget died; June 10th, Ken died; July 4th, Bruce died. These were all people that I knew very well through support groups, and I'll be thinking of them a lot today as we proceed. Thank you.

DR. SEO: Thank you, Mr. Weston.

Next we have our acting industry representative, Dr. Dayno.

DR. DAYNO: Good afternoon. My name is Jeffrey Dayno. I'm a neurologist, and I am the chief medical officer at Harmony Biosciences. Today I am serving as the industry representative on the panel for this advisory committee meeting. Thank you.

DR. SEO: Thank you.

We'll now go to our FDA participants. I'll begin with Dr. Dunn.

DR. DUNN: Good afternoon. I'm Dr. Billy Dunn. I'm the director of the Office of Neuroscience at the FDA.

DR. SEO: Thank you.

Next is Dr. Buracchio.

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

DR. SEO: Thank you.

And finally, we have Dr. Freilich.

DR. FREILICH: Hi. This is Dr. Emily Freilich. I'm the cross-discipline team leader for this application.

DR. SEO: Thank you all.

Dr. Montine?

DR. MONTINE: Thank you.

For topics such as those being discussed at this meeting, there are often a variety of opinions, some of which are quite strongly. Our goal is that this meeting will be a fair and open forum for discussion of 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 chairperson. 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.

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

Conflict of Interest Statement

DR. SEO: 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, or FACA, 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 the 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 the discussion of new drug application, or NDA, 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.

This is a particular matters meeting during which specific matters related to Amylyx Pharmaceuticals', Incorporated NDA will be discussed. Based on the agenda for today's meeting and all financial interests reported by committee members and temporary voting members, no conflicts of interest waivers 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. Jeffrey Dayno is participating in this meeting as a non-voting industry representative acting on behalf of regulated industry. Dr. Dayno's role at this meeting is to represent industry in general and not any particular company. Dr. Dayno is employed by Harmony Biosciences.

We would like to remind members and temporary voting members that if the discussions involve any other products 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?

DR. MONTINE: We will proceed with FDA introductory remarks by Dr. Billy Dunn.

Dr. Dunn, please?

FDA Introductory Remarks – Billy Dunn

DR. DUNN: Thank you, Dr. Montine.

Good afternoon, and welcome to our committee members and guests who are joining us today for this important meeting. I want to thank the committee for your willingness to be here, your eagerness to consider the important topics we will discuss today, and your forthrightness in sharing with us your perspectives on the application under consideration.

I particularly want to note and thank those affected by ALS who are joining us today. For those of you who have requested an opportunity to address the committee or who have provided written comments for the committee, we look forward to and are deeply appreciative of your input. Your efforts to join us are invaluable and tremendously

appreciated. Thank you.

We are here today to continue the discussion of AMX0035 for the treatment of patients with ALS. ALS is a devastating condition with a significant unmet medical need. Although there are three approved drug products, two of which are different formulations of the same entity, and the development pipeline is active, we are highly sensitive to the urgent need for the development of new treatments for ALS.

Before briefly 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. Conclusions and recommendations that you may have encountered during the proceedings of the prior meeting and during your review of the background materials for today's meeting, and that you may encounter during the upcoming presentations and discussions, should be viewed as preliminary considerations. The reason we are here today is to gain your input into some of the issues we have confronted during our

review process so that we may incorporate it into our ultimate decision on approvability.

We have reconvened the committee to continue discussion of the application in the context of additional information submitted by the sponsor. Following the initial committee meeting in March, the sponsor submitted additional analyses of the survival data from the CENTAUR study and its open-label extension, along with biomarker results from a recently completed phase 2 study of AMX0035 in Alzheimer's disease.

The sponsor positioned these data as a contribution to the confirmatory evidence intended to support approval. Accordingly, we extended the review period of the application to allow for adequate consideration of this new information. Recognizing the substantial unmet medical need in ALS, we feel that it is important that the committee is afforded the opportunity to consider this new information, along with the information presented at the prior AC meeting, in that context.

Scientists at FDA have reviewed the

additional information submitted by the sponsor in great detail, and several members of our team will share their thoughts with you today. Following my comments and a series of presentations by the sponsor, you will hear from three members of our team.

Dr. Teresa Buracchio, the director of the Division of Neurology 1, will provide an overview of the prior discussion of this application, an introduction to the new information submitted by the sponsor, and a discussion of important regulatory considerations and context. Dr. Tristan Massie, a statistician from the Division of Biostatistics 1, will present commentary on the sponsor's new survival analyses. Dr. Emily Freilich, the cross-discipline team leader for this application, will discuss the sponsor's new biomarker data from an Alzheimer's disease study.

As the committee will recall, the sponsor submitted results from the CENTAUR study, a double-blind, placebo-controlled, phase 2 study in 137 patients with ALS. This was a successful

study. It achieved a statistically significant result on its prespecified primary endpoint, which was verified by our team. Our review, however, raised analytical and interpretive concerns that limited any additional strong support from the placebo-controlled portion of CENTAUR beyond the primary endpoint. Although our concerns did not undermine the primary result, they did suggest that CENTAUR was not a highly persuasive trial.

The sponsor also submitted a post hoc survival analysis of an open-label extension of CENTAUR, the results of which suggested a survival benefit in patients that originally received AMX0035 compared to patients that originally received placebo. Our review again raised concerns regarding the interpretability of this finding.

Similar to the primary result, our concerns did not undermine the reported survival benefit, but did note that the effect on survival was not statistically persuasive and called into question whether the observed survival benefit could fairly be attributed to an effect of the drug. Thus, the

sponsor presented placebo-controlled data from one successful but not highly persuasive study, accompanied by confirmatory evidence of the survival benefit from an open-label extension study with notable interpretability challenges.

Given the critical review issue concerning whether the drug's effectiveness had been established by this combination of one double-blind, placebo-controlled study, plus confirmatory evidence from the open-label extension, this was the focus of the prior committee meeting, and the committee was asked to vote on whether these data established a conclusion that AMX0035 was effective for the treatment of ALS. Four committee members voted yes and six committee members voted no.

It is our goal today to build on the previous meeting by considering the additional information submitted by the sponsor against the background of the prior discussion.

Following the previous committee meeting, the sponsor submitted new information intended to

contribute additional confirmatory evidence to support approval. First, the sponsor performed an additional individual responder analysis of progression rate that uses participants as their own controls and compares the response rate in the AMX0035 group to the response rate in the placebo group.

As discussed in our background materials, this analysis has substantial interpretive challenges and is highly correlated with the primary analysis. It does not appear to be an appropriate analysis to provide confirmatory evidence of the CENTAUR primary result.

Second, the sponsor provided additional analyses of survival intended to complement the original survival analysis. These analyses are intended, in part, to account for the treatment crossover that occurred as placebo patients entered the open-label extension and use a combination of statistical methodologies and comparisons to external populations in an attempt to more fully explore the possibility of a survival benefit

attributable to AMX0035.

In brief, the sponsor asserts that the results of these analyses strengthen the previously reported survival benefit. Dr. Massie will discuss a variety of concerns and limitations associated with these analyses in his presentation on statistical considerations.

Third, the sponsor submitted a summary of exploratory analyses of a variety of CSF biomarkers from a placebo-controlled study of AMX0035 in Alzheimer's disease. Although several of these biomarkers showed nominally significant differences between treatment groups and appear potentially promising as possible evidence of pharmacodynamic activity, the character and relevance of these biomarker findings does not appear to provide clear evidence of a potential for clinical benefit in patients with ALS. Dr. Freilich will discuss these findings in greater detail.

It is vital to fully consider several issues when considering the data before us. They include the relevant approval pathway and standards; the

seriousness of the disease; the unmet need; and regulatory flexibility. Approval requires a demonstration of substantial evidence of effectiveness.

Although such evidence may come from a single study in isolation when the evidence provided by that study is felt to be sufficiently persuasive, it typically comes from more than one study; either in the form of two independent studies that serve to mutually substantiate their results, or in the form of one study with confirmatory evidence providing the independent substantiation of the study's results. It is the latter situation that is the subject of this marketing application, one successful study plus confirmatory evidence.

It is important to note that when considering one study plus confirmatory evidence, the single study that is involved in that situation may be a study of conventional persuasiveness rather than the highly persuasive study we prefer to see when considering a true single study in

isolation. The degree of persuasiveness required for approval may be influenced by many things, including the seriousness of the disease, whether there is an unmet need, and the character of the confirmatory evidence.

The serious nature of ALS contextualizes our consideration of the strength of evidence being presented in support of the effectiveness of AMX0035. ALS is a devastating, relentlessly progressive disease that is serious, severely debilitating, and life-threatening. Additional context is further provided by the tremendous unmet medical need for new treatments for ALS. Although there are approved therapies, their effects are limited, and new therapeutic agents are desperately needed.

Finally, regulatory flexibility is a prominent factor in our consideration of these data. It is important, critically so, and deserving of some focused discussion. Our underlying legal authority is clear and not only allowing but also endorsing and encouraging the

application of regulatory flexibility in the setting of serious and life-threatening diseases. It is unquestionably relevant to ALS drug development, in general, and to our specific consideration of the data before us.

From CFR 314.105(c), which discusses the general review and approval of all new drug applications, not simply those for serious and life-threatening conditions, quote, "FDA will approve an NDA after it determines that the drug meets the statutory standards for safety and effectiveness. While the statutory standards apply to all drugs, the many kinds of drugs that are subject to the statutory standards and the wide range of uses for those drugs demand flexibility in applying the standards.

"Thus, FDA is required to exercise its scientific judgment to determine the kind and quantity of data and information an applicant is required to provide for a particular drug to meet the statutory standards," end quote. It is apparent from this that regulatory flexibility is a

foundational construct.

From CFR 312.80, which discusses drugs intended to treat life-threatening and severely debilitating illnesses and makes explicit reference to 314.105(c), which I just reviewed, quote, "The purpose of this section is to establish procedures designed to expedite the development, evaluation, and marketing of new therapies intended to treat persons with life-threatening and severely debilitating illnesses, especially where no satisfactory alternative therapy exists.

"As stated in CFR 314.105(c) of this chapter, while the statutory standards of safety and effectiveness apply to all drugs, the many kinds of drugs that are subject to them and the wide range of uses for those drugs demand flexibility in applying the standards.

"The Food and Drug Administration has determined that it is appropriate to exercise the broadest flexibility in applying the statutory standards while preserving appropriate guarantees for safety and effectiveness. These procedures

reflect the recognition that physicians and patients are generally willing to accept greater risks or side effects from products that treat life-threatening and severely debilitating illnesses than they would accept from products that treat less serious illnesses. These procedures also reflect the recognition that the benefits of the drug need to be evaluated in light of the severity of the disease being treated," end quote.

This makes it abundantly clear that for these serious diseases like ALS and so many other neurological conditions, the maximum degree of regulatory flexibility, quote, "the broadest flexibility in applying the statutory standards," end quote, is operational.

From CFR 312.84, which discusses the risk-benefit analysis in review of marketing applications for drugs to treat life-threatening and severely debilitating illnesses, and makes explicit reference to 312.80, which I just reviewed, quote, "FDA's application of the statutory standards for marketing approval shall

recognize the need for a medical risk-benefit judgment in making the final decision on approvability. As part of this evaluation, consistent with the statement of purpose in CFR 312.80, FDA will consider whether the benefits of the drug outweigh the known and potential risks of the drug, and the need to answer remaining questions about risks and benefits of the drug, taking into consideration the severity of the disease and the absence of satisfactory alternative therapy," end quote.

From the 2019 FDA draft guidance on Demonstrating Substantial Evidence of Effectiveness for Human Drug and Biological Products, quote, "In all cases, FDA must reach the conclusion that there is substantial evidence of effectiveness to approve a drug. However, the degree of certainty supporting such a conclusion may differ depending on clinical circumstances; for example, severity of the disease and unmet medical need," end quote. The guidance goes on to discuss in a variety of ways the recognition that a greater risk of false

positive conclusions may be acceptable.

So not only is regulatory flexibility a well-recognized concept, but it is found throughout our regulatory framework. But what is it? Some are accustomed to thinking of regulatory flexibility as granting more numerous formal meetings with sponsors to ensure adequate discussion of a complicated topic; entertaining novel outcomes supported by less-than-ideal data; accepting requests for a rapidly scheduled call with a sponsor to provide clarity on a topic that was left unresolved at a previous meeting; and the list goes on.

But these are the easy examples. The more challenging application of regulatory flexibility concerns the need to tolerate a greater degree of residual uncertainty when making a subjective decision on approval. In appropriate circumstances such as serious and life-threatening diseases in settings of substantial unmet need, regulatory flexibility applied to assessments of effectiveness means increased tolerance for concluding that a

drug is effective when there is residual uncertainty that the drug may not actually be effective, which would be a conclusion at risk of being a false positive, and decreased tolerance for concluding that a drug is ineffective when there is residual uncertainty that the drug may actually be effective, which would be a conclusion at risk of being a false negative.

Have we done this in ALS? We most certainly have. Both of our novel approvals were based on the application of substantial regulatory flexibility. Riluzole was approved in 1995, based on two studies that failed. Both studies failed to demonstrate statistically significant findings on the primary endpoint of survival using the prespecified analysis. No functional benefit was seen.

FDA decided another analytical method was more appropriate and conducted alternative, exploratory, post hoc analyses that resulted in approval despite additional interpretive challenges that emerged with the exploratory analyses. The

approval memorandum stated that the beneficial effects were small, transient, clinically undetectable, and that the evidence is far from strong.

Edaravone was approved in 2017, based on a single non-U.S. study of 137 patients in Japan. The persuasiveness of the primary outcome was quite strong, using the prespecified analytical method, and sensitivity analyses provided strong support for the primary analysis. Secondary outcomes, generally but not uniformly, trended and supported the primary analysis, but were not significant. There are no data on survival benefit. The study had several characteristics that were felt to make it appropriate to consider as a single study. The approval memorandum notes that a high degree of flexibility was applied because of the unmet need.

So it is clear that regulatory flexibility is a fundamental aspect of our general regulatory framework, and that we are familiar with its considerations and the neurological space, and it has played a direct role in the ALS drugs that we

have approved to date. Notwithstanding the complexities and challenges of comparing results across different programs, these two approvals are a relevant precedent when considering the data supporting this application.

We find ourselves in a situation, both straightforward and complex, reasonably straight forward to describe; somewhat complex to consider.

First, the straightforward. We have a single successful study. That study is not exceptionally persuasive for a variety of reasons, thus making it unsuited to support approval in isolation without any support from accompanying studies or confirmatory evidence. This appears to be a reasonable stance even when considering the results of the study in the context of regulatory flexibility.

For the reasons discussed with the committee previously, it does not appear possible for the study alone to meet the requirements for substantial evidence, however, the study does not exist in isolation. It is accompanied by

additional data positioned as confirmatory evidence. At the time of the previous committee meeting, this confirmatory evidence took the form of a single exploratory analysis of survival. Interpretation of that analysis was hampered by many issues that were previously presented to the committee.

Since the previous meeting, additional analyses of the survival data, based on different methodological approaches, have been conducted by the sponsor and submitted as additional confirmatory evidence. These new analyses are encumbered by many of the same issues that affected the initial survival analysis, along with additional interpretive challenges of their own.

Notwithstanding all these issues, a report of survival benefit was and remains an important part of the consideration of this application. The sponsor has also provided new evidence of pharmacodynamic activity in another disease. Though promising in terms of biological activity, it is of unclear relevance to ALS.

Taking the two together, the data provided by the CENTAUR study and the accompanying confirmatory evidence intended to together establish substantial evidence are expanded from those considered at the prior meeting.

Now, the complex. Given that the current data are complicated to interpret, even in the setting of regulatory flexibility, the ongoing phase 3 PHOENIX study takes on great relevance and importance. The committee will recall the prior discussion of the PHOENIX study. We have again described it in our background materials, and it will be discussed in our later presentation.

Essentially, we have a binary decision to make on the current application with regard to approval, and there will be a binary future outcome of the PHOENIX study with regard to success, resulting in four situations that one may envision.

The two situations in which a potential decision on approval, or non-approval, and the future outcome of PHOENIX are concordant with regard to the effectiveness or ineffectiveness of

AMX0035 may be dismissed as conceptually non-controversial for the purposes of discussion. It is the other two situations that merits scrutiny, discussion, and careful consideration. In these situations in which a potential decision on approval, or non-approval, and the future outcome of PHOENIX are not concordant, both situations would have endorsed a false conclusion that would require a remedy.

Working on the assumption that the large PHOENIX study will provide a more definitive result than we currently have available, the future PHOENIX outcome raises the possibility that a decision based on a conclusion regarding the effectiveness or ineffectiveness of AMX0035 on the basis of the data in front of us today may in fact ultimately be shown to represent a false positive or a false negative.

In the false negative setting of non-approval but later success in PHOENIX, the remedy would appear obvious. Although some might reasonably argue that substantial evidence does not

currently exist, resulting in non-approval, it would seem that most would find that the combination of the current data and a future successful PHOENIX study would clearly constitute substantial evidence. The remedy in that situation would be future approval based on that combination of data.

In the false positive setting of approval followed by an unsuccessful PHOENIX, the remedy may not seem quite so obvious, as the drug would already have been approved based on the current data There is in fact a remedy for this situation. Under CFR 314.150, FDA has the authority to withdraw approval of a drug if it finds, upon the basis of new information before FDA with respect to the drug, evaluated together with the evidence available when the application was approved, that there is a lack of substantial evidence that the drug will have the effect it is represented to have in its approved labeling.

Said differently, the law recognizes that a finding of substantial evidence of effectiveness

sufficient to support approval is not a static fixed conclusion, unamenable to future consideration when confronted with new data that calls the original justified conclusion into question.

Indeed, this is conceptually consistent with the regulatory environment of other health authorities. Since the last committee meeting, AMX0035 was approved in Canada under a pathway commonly known as conditional approval. We have included information on this approval pathway in the background materials, and Dr. Buracchio will be speaking about it in more detail later.

But briefly, this Canadian approval, known as a notice of compliance with conditions, is based on promising evidence rather than substantial evidence and is predicated on the successful outcome of a confirmatory study; here, the PHOENIX study. If the confirmatory study fails or is not completed, the conditional approval may be withdrawn.

The company has clearly indicated its

awareness of the relevance of the PHOENIX study, stating publicly that it understands that continued approval in Canada is contingent upon success in PHOENIX. Arguably, that should make it easy for the company to make a similar public statement concerning the prospect of an approval of the current application.

Given that a company can choose to voluntarily withdraw a product for marketing, it would seem that the committee may be interested in a clear understanding of the sponsor's intent in seeking approval now while PHOENIX is ongoing, and I call on the company's co-CEOs to state for the committee whether the company would voluntarily withdraw the product from marketing if the PHOENIX study does not succeed should their current application ultimately be approved.

This request should in no way be interpreted as suggesting that we have reached a decision on the application. It is simply a request for important contextual information for the committee's consideration, especially given the

numerous comments by committee members at the last meeting regarding the importance of the ongoing PHOENIX study.

The final consideration regarding the complex aspects of this situation is to consider the role of regulatory flexibility. As I discussed previously, FDA has determined that it is appropriate to express the broadest flexibility in applying the statutory standards for drugs intended to treat life-threatening and severely debilitating illnesses.

The statutory standard of substantial evidence of effectiveness is a qualitative standard; it is not a quantitative standard. Achieving statistical significance is not in the definition of substantial evidence. While statistical considerations are one factor that plays into our deliberations, scientific judgments taking into account many factors, including the context of the disease, is needed to determine whether substantial evidence of effectiveness exists. Your discussion today will play an

important role in that determination.

Today we are explicitly asking you to discuss the complexities of this situation as a committee. We will be listening carefully to the conversations you have with each other. We are interested in how you approach and discuss differences of opinion. Today we have attempted to provide you with information that will hopefully serve you well in a conversation about complicated data as you consider the strength of the efficacy information and whether the benefit is sufficient to support approval.

We have formulated a question designed to allow for this committee to advise us on this point. We expect you to discuss whether and how you have considered the serious nature of ALS, the unmet need in the disease, and the ongoing PHOENIX study. We encourage you to discuss the role of flexibility in your assessments and how it does or does not influence your considerations. After this first discussion period is concluded, we will be asking you to vote on whether you feel approval is

warranted.

It is the combination of your preceding discussion and your vote with accompanying explanation that will provide advice of great value to us. We recognize that you carefully reviewed the materials previously and provided us with a thoughtful vote and commentary. We hope that we have provided you with additional information today to bring you up to date on the sponsor's submission, and that we have provided you with the background information that you need to consider whether you do or do not favor approval of the drug.

Again, no final decision has been made on approvability, and we very much look forward to the insights you will provide. We have reconvened this committee because we believe that a final decision requires your input and advice. Thank you for the substantial efforts 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. Dunn.

Both the Food and Drug Administration 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 the 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 this issue of financial relationships at the beginning

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

We will now proceed with Amylyx's presentations.

MR. KLEE: Before we begin our formal presentation, this is Justin Klee, co-CEO and co-founder of Amylyx Pharmaceuticals, and with me is Joshua Cohen, co-CEO and co-founder of Amylyx Pharmaceuticals.

Thank you, Dr. Dunn, for your remarks, and we would like to address them. To be clear, if PHOENIX is not successful, we will do what is right for patients, which includes voluntarily removing the product from the market.

And now I'd like to hand it over for our formal presentation to Tammy Sarnelli.

Applicant Presentation – Tammy Sarnelli

MS. SARNELLI: Good afternoon. I'm Tammy Sarnelli, global head of Regulatory Affairs at Amylyx Pharmaceuticals. I want to thank you all for your time today, and thank the FDA for the invitation to review new and important data with

this committee. I also want to acknowledge the thousands of people living with ALS for your continued perseverance and resilience.

Before discussing the new data, let me remind the panel of the focus of the last meeting. As the agency noted in their briefing document, CENTAUR met its prespecified primary outcome as measured by the ALSFRS-R, an endpoint considered acceptable by FDA to support approval. Over long-term follow-up, AMX0035 also demonstrated a 4.8-month median overall survival benefit.

The question today is how this fits into the framework of substantial evidence of efficacy. Of course, one pathway is to have two studies. Another way is to have a single study. Let me review the regulatory pathways for a single study.

The FDA has concluded that a single, adequate, and well-controlled trial is sufficient to establish effectiveness when it is either highly statistically persuasive or supported by confirmatory evidence, as confirmatory evidence may help substantiate findings of benefit. In

addition, as stated in FDA's briefing document and their own guidance, FDA can exercise broad scientific judgment in applying the evidentiary approval standards to drugs for life-threatening and severely debilitating diseases such as ALS. Today we are discussing this pathway, a single positive study with confirmatory evidence.

The CENTAUR study is a positive, adequate and well-controlled trial, as it met its prespecified primary endpoint. There are many acceptable types of confirmatory evidence for this result, and while overall survival is rarely assessed in neurological diseases given their typical progression, it is considered the gold standard in fatal diseases because it is unambiguous and unquestionably clinically meaningful. This is relevant in ALS, a uniformly fatal disease where average survival is just two years after diagnosis.

The FDA has cited in their 2017 guidance, quote, "For many serious diseases, there is an endpoint of such great clinical importance that it

is unreasonable not to collect and analyze the endpoint data; the usual example is mortality," end quote. Thus, our ITT overall survival data serves as confirmatory evidence.

At the last advisory committee meeting, we presented the ITT overall survival data showing a 4.8-month survival benefit, using a conservative analysis that does not take treatment crossover in the placebo group into account. In the face of such an important finding, one would wish to confirm that the observed benefit is indeed robust.

The FDA's framework in the 2019 substantial evidence guidance provides ways to evaluate and confirm a survival benefit. As noted in the guidance, survival may be ascertained using either concurrent or external controls, and may be further confirms by data from separate sources such as natural history.

Thus, to further support the ITT overall survival benefit, we conducted three new survival analyses using three different and independent control groups. The first is a new analysis that

adjusts for the placebo crossover effect, and we have two additional analyses with new external controls. All analyses show a treatment benefit on survival, with the new analyses suggesting that the treatment benefit seen may be even greater than what was observed in the ITT overall survival analysis in CENTAUR.

No matter the analysis, no matter the control group, all four analyses find the same thing; that people with ALS on AMX0035 live substantially longer than people with ALS on standard of care. These data, in addition to meeting the primary endpoint, serve to establish substantial evidence of effectiveness and are in line with precedents and regulations outlined by the FDA.

I want to touch briefly on our ongoing phase 3 PHOENIX trial. I should note that FDA asked us to submit our NDA based on CENTAUR alone and before the start of PHOENIX. We continue recruiting and currently have enrolled more than 350 participants in approximately 65 sites across

the globe. Completion of this trial is part of our conditional approval in Canada, as well as our review in Europe. Conditional approval is restricted to promising new drug therapies for the treatment of serious or life-threatening diseases where the new product represents a significant improvement in benefit-risk over existing products.

We are committed to rapidly and diligently completing PHOENIX. Results from this 48-week, placebo-controlled study will be available and reportable to regulatory agencies by mid-to-late 2024. If AMX0035 is not approved now, the FDA anticipated decision will likely happen in 2025, underscoring the critical importance of today's outcome.

Given the FDA's request, today's presentation will focus on the new overall survival evidence we have submitted to the agency. We will however provide a brief overview of the primary endpoint results to help put these data into context; and while not provided as confirmatory evidence, we will briefly present new biomarker

data to shed light on the mechanistic activity of AMX0035. And because it's important to evaluate the strength of the AMX0035 data within the current landscape of ALS, Dr. Paganoni and Dr. Cudkowicz will both provide their perspective on these important topics.

We also have several additional experts with us today to help address your questions. These include Dr. Bowser, chief scientific officer and professor at the Barrow Neurological Institute; Dr. Schoenfeld, professor emeritus, Harvard Medical School; Dr. Robins, Dong Professor of Epidemiology at the Harvard T.H. Chan School of Public Health; Dr. Hendrix, CEO of Pentara; and Dr. Quintana, senior statistical scientist at Berry Consultants.

We also have two clinical experts and leading ALS researchers, Dr. Berry, director of the MGH Neurological Research Institute; and Dr. Shefner, senior vice president and Kemper and Ethel Marley Professor of Neurology at the Barrow Neurological Institute. These outside experts have been compensated for their time preparing for

today's meeting.

Thank you very much, and I'll now turn the presentation over to Dr. Paganoni.

Applicant Presentation – Sabrina Paganoni

DR. PAGANONI: Hello. I'm Sabrina Paganoni, 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 then 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 PHOENIX trial.

As the PI of the coordination center of the CENTAUR trial, I have received grant funding from Amylyx, and as a co-chair of the ongoing PHOENIX trial, I am receiving institutional consulting support for my time. And I'm here today to provide some brief background on ALS and importantly what matters to people with ALS, which is living longer and having more time with their families.

ALS is an awful disease. By the time I've

diagnosed someone with ALS in my clinic, they are already experiencing a series of unrelenting and irreversible losses. The patient, 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 patient go from walking on their own, to using the cane, to needing a wheelchair; from breathing on their own, to requiring assisted ventilation, to meeting with hospice. Median survival is only around two years from diagnosis.

Patients tell us that they want to retain independence, but once this function is lost, it cannot be regained, and the next loss is already underway. 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.

There are only two approved products for treating ALS, riluzole and edaravone. Riluzole was approved by the FDA in 1995. In the original trials, riluzole showed a survival benefit of 2 to

3 months and no effect on function. After over 20 years, edaravone was approved in 2017. In the trial that led to approval, edaravone slowed functional decline with no effect on survival. So the mainstay of care for my patients is timely intervention to manage symptoms and initiating these drugs when appropriate.

I've been treating people with ALS for a decade, and while I'm thankful for the two products and the regulatory flexibility that was utilized in their approval, I can tell you that what we have is not sufficient. The pressing need for new treatments is part of why my colleagues, my patients, and I are excited about AMX0035, but that's not the main reason. The main reason is the data.

In the CENTAUR trial, AMX0035 showed a significant and clinically meaningful impact on endpoints that matter, both function and survival. CENTAUR met its prespecified endpoint. Treatment with AMX0035 resulted in slowing of disease progression and retention of functional

independence, and given that the ALSFRS-R measures functional independence, it's not surprising that it has shown correlation with quality-of-life measures.

We also saw a significant delay in the time to first hospitalization and time to tracheostomy or permanent assisted ventilation, and these outcomes culminated in the key endpoint, longer survival. Each endpoint on its own is important and meaningful. Taken together, the results are compelling and an important addition to current standard of care.

Let me briefly touch on why these results are also exciting for the field of ALS clinical research. While the methods used to analyze survival in CENTAUR may be new to the field of ALS, they are aligned with FDA ALS guidance, and they are the direction we're heading in. And while this is probably the first time that results from an open-label extension are included in an application for ALS, it certainly won't be the last.

We used robust processes to capture survival

in CENTAUR. The ITT overall survival analysis has essentially no missing data, and all participants and investigators were blinded through the end of survival follow-up. This allowed for a placebo-controlled analysis of overall survival. We were also able to leverage external controls to further understand the impact of AMX003535 on survival thanks to many of my colleagues who have conducted large-scale natural history studies that allow us to understand expected disease progression and predictors of survival.

Today large data sets are available that include data from thousands of people whose disease trajectory has been carefully captured in clinic or in the context of previous ALS clinical trials, and I'm referring specifically to the ENCALS clinic database and to the PRO-ACT clinical trial database. The existence of these resources allowed us to further analyze the benefit of AMX0035 on survival.

What is exciting is the significant progress the academic community is making on biomarkers.

This is still an evolving field. There is a lot that we know and a lot that we still need to learn to best use candidate biomarkers for diagnosis, prognosis, and to measure response to treatment. Biomarkers that capture various aspects of ALS are emerging and are becoming an important readout in clinical studies.

Neurofilaments are the biomarkers with the largest body of evidence to date, and data show that these markers correlate with prognosis in people with ALS. But many other promising biomarkers are also emerging in ALS, as shown on this slide. This highlights that ALS is a multifaceted disease, and different biomarkers will capture different aspects of disease pathology.

To close, we urgently need new treatment for ALS. People with ALS have a short life expectancy, and there is no cure. By the time someone is diagnosed with ALS, their symptoms have already started to take over and they quickly lose independence. People with ALS tell us that they want to retain function for as long as possible.

The two currently approved treatments for ALS show either a benefit on survival or a slowing in functional decline, but neither has demonstrated both in the trials that led to their approval. The results from the CENTAUR trial are positive and robust. To have a drug like AMX0035 that help people live longer and extend their functional ability while they're living is exactly what this community has been waiting for.

The field of ALS is evolving and exciting things are happening, including in the way we design and analyze data from trials and what we're learning on biomarkers. And why the latter is exciting, what is most important to me is clinical evidence, which AMX0035 has clearly demonstrated.

Thank you for your attention, and I'll now turn the presentation over to Dr. Mehta.

Applicant Presentation – Lahar Mehta

DR. MEHTA: Thank you, Dr. Paganoni.

I'm Lahar Mehta, head of Global Clinical Development at Amylyx Pharmaceuticals. Today I want to briefly expand on Dr. Paganoni's remarks on

biomarkers and discuss some new biomarker data, showing the biologic and mechanistic activity of AMX0035.

To date, Amylyx has completed two clinical trials. CENTAUR was the first trial in ALS, where plasma samples were collected for biomarker analysis. Neurofilaments were assessed as a prespecified secondary endpoint. When CENTAUR was designed, biomarkers in ALS were less developed, so additional plasma samples were stored for future analysis of emerging biomarkers.

Given that the mechanism of action of AMX0035 is applicable across many neurodegenerative conditions, we also explored the impact of AMX0035 in Alzheimer's disease in the 24-week exploratory study, PEGASUS. In PEGASUS, CSF samples were obtained to explore the impact of AMX0035 on a prespecified group of biomarkers relevant to Alzheimer's disease and other neurodegenerative conditions. Starting with the results from PEGASUS, AMX0035 improves several CSF biomarkers in Alzheimer's disease over a period of 24 weeks,

providing mechanistic evidence that AMX0035 is active against several key neurodegenerative processes.

Here, I am showing some of the most relevant biomarkers that improved. A decrease represents an improvement, except for the A-beta 42 to 40 ratio where an increase is an improvement. Overall, AMX0035 showed a nominally significant improvement across multiple biomarkers. There were a number of biomarkers that did not improve, including neurofilament, and these are shown in the briefing document.

It is worth noting that a significant reduction was observed in YKL-40. Recent literature supports the potential of YKL-40 as a prognostic marker in ALS. Therefore, we recently conducted an exploratory analysis from the stored samples from the CENTAUR study to examine whether AMX0035 improves plasma levels of YKL-40 in ALS in addition to Alzheimer's. I will now show some of the new preliminary data generated in the CENTAUR ALS trial using the stored plasma samples.

As we can see, there was a significant difference in YKL-40 plasma levels, favoring treatment with AMX0035, representing a 20 percent reduction compared to placebo. Previous studies have shown that YKL-40 correlates with ALS disease progression rate, severity, and survival. This correlation was supported by the data from the CENTAUR study, as we both see a correlation for YKL-40 levels to ALSFRS-R score, as well as progression rate.

These new biomarker results are interesting and support the biologic impact of AMX0035, but our focus today is on the clinical evidence and how that constitutes confirmatory evidence. For that, I will turn the presentation to Dr. Timmons.

Applicant Presentation – Jamie Timmons

DR. TIMMONS: Thank you, Dr. Mehta.

I am Jamie Timmons, head of Scientific Communications at Amylyx. As Ms. Sarnelli reviewed, there is a clear and established pathway for meeting the regulatory standard of substantial evidence of effectiveness based on a single,

adequate, well-controlled trial, plus confirmatory evidence. Let's review the comprehensive data showing that AMX0035 meets this standard.

In terms of meeting the first criteria of an adequate and well-controlled trial, CENTAUR was a rigorous study conducted with ALS experts across 25 sites in the United States. CENTAUR met its prespecified primary outcome. There is confirmatory evidence for this primary finding in the results of the ITT overall survival analysis, which shows an almost 5-month longer survival for the AMX0035 group. Robustness of the survival benefit is further supported by new analyses that utilize three different control groups.

Despite different methodologies, each of these new analyses yield a consistent finding, confirming the ITT overall survival benefits of AMX0035. The data from CENTAUR support substantial evidence of effectiveness of AMX0035 in ALS.

Let's start first with a brief recap of the CENTAUR study primary outcome model. AMX0035 met its primary endpoint, showing a 25 percent

reduction in the rate of progression of the ALSFRS-R compared to placebo. Importantly, the separation began as early as week 6 and was sustained through week 24. This effect was seen on top of standard-of-care use of approved ALS medications riluzole and edaravone.

There is limited published data on what constitutes a clinically meaningful change in the ALSFRS-R. The main study often cited is a survey of 65 ALS experts in the U.S. that found that most would consider a 20 percent change in the rate of decline of the ALSFRS-R total score as clinically significant.

The robustness of the primary analysis finding is supported by several sensitivity analyses that evaluate the impact of primary model assumption, concomitant medication use, and in-study deaths. All analyses yield a treatment effect that is consistent with the primary model.

Starting with model assumption, a shared baseline, linear, mixed-effect model was used for CENTAUR. Sensitivity analyses abandoning the

shared baseline and linearity assumption both remained consistent with the primary analysis results. The impact of concomitant use of ALS medications riluzole and edaravone was also evaluated, showing that the beneficial effects of AMX0035 on ALSFRS-R was consistent after adjusting for time on each medication.

Additionally, a new analysis was performed that removed participants with in-study edaravone starts. This analysis showed a consistent treatment effect of a 2.4 point difference and a p-value of 0.04, again, indicating that the results seen with AMX0035 was independent of concomitant medications.

We have previously discussed the rationale for choosing this primary model and not a joint-rank model. As noted during the first advisory committee, the choice to use the shared baseline, linear, mixed-effects model, and not joint rank, was done in collaboration with the co-inventor of the joint-rank method, the key rational being, among other factors, that

simulations confirm that the joint-rank method is less sensitive when there is expected to be a limited number of participant deaths during the analysis period, which is exactly what was expected and occurred during the first 24 weeks.

So putting that rationale and background aside, we agree that it is important to assess for the impact of in-study deaths and performed several sensitivity analyses to evaluate the impact of mortality on the primary endpoint result. Every analysis is consistent with the results of the prespecified primary efficacy analysis, including joint-rank analyses, where as discussed during the last meeting, both Amylyx and FDA get a p-value of 0.05 when performing a joint-rank analysis on the prespecified mITT population.

These results support that the primary outcome was analyzed using appropriate methods and is robust and consistent across sensitivity analyses, evaluating different assumptions.

With CENTAUR meeting its prespecified primary endpoint, we now look to the data that

supports confirmatory evidence, starting with the ITT overall survival analysis. We did discuss this analysis last time. However, it is important to review in detail to ensure that the methodology is clear and that questions raised during the last meeting and by the FDA are answered, as the ITT overall survival result is the foundation for the additional analyses we will also present.

As a reminder, this is a randomized, placebo-controlled analysis with comprehensive data capture. Because data is captured even on participants who have dropped out of the study, dropouts do not impact this analysis. The baseline survival prognosis was well balanced between groups. The overall survival result was not impacted by concomitant medication use and was consistent across time points of analyses.

Let's first review some important methodology points. First, ITT overall survival analysis compares two groups, the 89 participants that started on AMX0035 to the 48 participants that started on placebo. Both investigators and

participants remained blinded to original treatment assignment through the duration of follow-up. As such, this is a randomized, placebo-controlled comparison.

The placebo group was able to cross over to receive AMX0035 after 24 weeks. Since the ITT analysis is simply comparing the two groups that started on AMX0035 versus placebo, it did not take the placebo crossover into account, but the new analyses we will present later do.

ITT overall survival analysis and the new analyses all use the treatment extension, last participant, last visit date of March 1, 2021 as the analysis cutoff date. Survival status was verified for nearly every participant in the study as of March 2021, 136 of 137 people. The single person whose vital status could not be determined was censored as of the date of last follow-up.

In the ITT overall survival analysis, a median survival difference of 4.8 months between AMX0035 compared to placebo and a 36 percent less risk of death at any specific time point is seen.

Same as the primary outcome, this difference is on top of standard-of-care use of riluzole and edaravone. Looking at this data further, there is a relationship between duration of exposure and survival. In a subgroup analysis, the group of participants who were on AMX0035 the longest had the longest survival. The group of participants who started placebo and never received AMX0035 in the treatment extension had the shortest survival.

I'll next review some additional data that supports this ITT overall survival finding. The first question many ask when they see this result is how well balanced are the two comparison groups. Looking at the baseline characteristics, the groups are well balanced in terms of key characteristics that are known to predict survival in ALS, specifically time since symptom onset; pretrial ALSFRS-R progression rate; baseline ALSFRS-R; breathing capacity as measured by SVC; and age. One is the new analyses also further demonstrates the balance between the groups at baseline. I'll point that out when we get to that data.

As noted, participants were allowed to continue standard-of-care use of riluzole and edaravone during CENTAUR. Most participants were taking either of the two at or prior to beginning the study, and so another logical question is how this concomitant medication use impacts the ITT overall survival result.

Sensitivity analyses were performed to assess the impact of concomitant use of riluzole or edaravone on the ITT results. As shown, these remained consistent when correcting for baseline use of these medications. Furthermore, an additional analysis that removed participants within study edaravone starts also showed consistent results with the ITT overall survival analysis.

FDA has raised that the survival analysis was performed at different cutoff dates. March 2021 corresponds to the last participant, last visit in the treatment extension and was requested by the FDA as the key time point for analysis for benefit-risk, so we have chosen to

present this as the main analysis. Regardless of cutoff dates, the survival benefit for AMX0035 was consistent, showing a hazard ratio between 0.57 to 0.64.

Finally, we note that survival is an outcome of special significance in clinical trials. In 2017 guidance about endpoints and statistical hierarchies, FDA recommends analyzing and placing weight on mortality regardless of the endpoint hierarchy due to the clear importance of this outcome. Even a suggestion of a favorable result is considered important. Here we have a benefit in the ITT population and the randomized, placebo-controlled analysis, which is nominally significant and clinically meaningful. That brings us to the new analyses.

As we just walked through, the ITT overall survival analysis has key strengths, specifically that it is a randomized, placebo-controlled analysis, and participant dropouts do not impact the data capture. Additional analyses were performed and shared with the FDA to further

independently support the robustness of the ITT overall survival result. One important benefit of these analyses is that they provide a new treatment-naive comparator group to allow an estimate of the full extent of the survival benefit. Each method is utilizing a different control arm. The observed survival of the 89 participants randomized to AMX0035 at the start of CENTAUR will be compared to each new control.

The first method adjusts the CENTAUR ITT overall survival placebo arm to remove the effects of treatment crossover. The other two methods used data external to the trials from key ALS data sources to create comparator control arms. The rationale for these analyses is not that one is better than the other, but rather that they provide complementary information when viewed in totality with the ITT overall survival result.

The first method adjusts the placebo ITT overall survival arm for treatment crossover and is known as the Rank Preserving Structural Failure Time Model or RPSFTM. The model calculates the

survival time gained by receiving AMX0035, and then adjusts the placebo arm to remove this gain. This is a method frequently employed in oncology clinical trials, where placebo group crossover is common. There is extensive supporting literature using this methodology to correct for placebo group treatment crossover, and data utilizing this methodology has been cited in FDA drug reviews and health technology assessments.

As opposed to the other two methods that use data external to the CENTAUR trial to create comparator control arms, the method is adjusting the original placebo group to account for treatment crossover. Hence, the comparison groups are the observed AMX0035 ITT overall survival arm and the placebo arm adjusted for crossover.

Analysis of the CENTAUR data using this methodology found that the estimated median survival benefit for AMX0035 was 9.7 months and the estimated hazard ratio was 0.42 in comparison to the ITT hazard ratio of 0.64. Looking at these results in a more visual way, the KM curve allows

us to compare the original placebo ITT results in gray with the crossover-adjusted placebo results in light blue; again, highlighting the even longer median survival difference between the crossover-adjusted arm and the original ITT AMX0035 arm in dark blue.

The core benefit of this analysis is that it estimates a treatment-naive placebo arm using a methodology that is well supported. The method does assume a common treatment effect regardless of timing of initiation of therapy. This is a reasonable assumption given that there is only 6 months before the placebo group crosses over to AMX0035.

To address points raised by the FDA, the briefing document states that simulation show that the RPSFTM can lead to large biases based on a publication by Latimer and colleagues. This simulation study cited generally finds that the maximum bias is less than 10 percent, which even in this worst case scenario would still result in a significant overall survival benefit of about

9 months.

FDA also questions why the p-value is the same as for the ITT analysis. The RPSFTM uses the p-value from the ITT analysis, so this is expected. Finally, FDA also recommends conducting other methods to look for consistency. We agree and will review these next, as we will share the other methods show consistency with the RPSFTM analysis, supporting the validity of this approach.

Moving over to the other two analyses that utilize external controls to compare the survival benefit with AMX0035; first the rationale behind doing so. As stated earlier, the 2019 Substantial Evidence of Effectiveness guidance lists natural history confirmation of survival as a type of confirmatory evidence. So with this support from the guidance, the next questions are, what is the best source of external control data in ALS, and how well matched are these sources to the CENTAUR population?

Fortunately, as Dr. Paganoni reviewed, there are substantial data sets that are the culmination

of large-scale collaborations that include survival data from thousands of people with ALS. The two sources utilized for our analyses are the European Network to Cure ALS, or ENCALS, clinic database and related Survival Prediction Model, and the Pooled Resource Open-Access ALS Clinical Trials or PRO-ACT database. I will share details on how well matched these two sources are to the CENTAUR population as we review each method further. Let's start with the first external control.

The first method uses the natural history ENCALS Survival Prediction Model to create a predicted survival control arm. This survival prediction model is validated, published in Lancet Neurology, publicly available, and uses data from more than 10,000 people with ALS from 14 specialized ALS centers across Europe. The model was developed and validated based on clinical, cognitive, and genetic predictors of tracheostomy-free survival. The predictors are listed in the table to the right. These predictors are relatively easy to capture in a clinic visit.

Authors looked at how well their model predicted survival in people with ALS. As shown in their validation publication, the models showed excellent agreement between predicted survival, the solid lines, versus observed survival, the dotted lines, in the validation cohort. As such, the predictions of survival from the model appear reliable and match observed results.

Moving now to the analyses done using this model on the CENTAUR survival data, using baseline characteristics from participants in CENTAUR, the originators of the model generated a predicted survival for each participant. They were blinded to treatment assignments when creating these individual predictions. Each prediction was then grouped per treatment assignment, which allowed for two key comparisons; first, comparing the predicted AMX0035 survival at baseline to the predicted placebo survival at baseline to see if the original treatment groups were well matched in survival prognosis. This is the additional evidence on baseline prognostic balance I mentioned earlier.

On this slide, we are looking at the predictions for the AMX0035 group versus the placebo group at baseline. We can see that the predicted probability of survival was very closely aligned. Two lines are essentially overlapping. This offers further support that the survival prognosis was well balanced at baseline between the groups in the ITT overall survival analysis. In addition to comparing the predicted prognosis for the groups at baseline, the model allows the comparison of the observed AMX0035 ITT overall survival and the predicted survival for that exact same group of participants.

This is the external control comparison. In this analysis, the observed ITT AMX0035 group showed a median survival of 23.5 months compared to 13.6 in the natural history survival prediction control arm, resulting in a median overall survival difference of 9.9 months. The estimated hazard ratio was 0.32 in comparison to the ITT hazard ratio of 0.64. Looking at these results in a more visual way with the KM curve allows us a different

view, again, showing the median overall survival difference of 9.9 months.

This natural history survival prediction model analysis allows comparison of the observed AMX0035 survival to a treatment-naive comparator using an independent external data set. I've noted such data is specifically listed as a type of confirmatory evidence in FDA guidance.

The results seen with this different methodology are remarkably close to the first method using the crossover adjusted to the placebo arm, supporting the robustness of both approaches. While the model was built using data from European people with ALS from a clinic population, a recent review assessing region-specific guidelines and ALS management in the U.S., Europe, and Japan do not find substantial regional differences in rate of disease progression and approaches to multidisciplinary care, indicating that regional differences are unlikely to lead to a large bias.

FDA's concerns around this analysis primarily relate to whether this model can reliably

estimate survival. As the validation work showed, this model is indeed reliable in estimating survival. FDA also comments that differences could arise as participants in the ENCALS model were not in clinical trials. We have also conducted an analysis using a primarily U.S. ALS clinical trial population. Let's review that next.

Data source for the second external control arm is the PRO-ACT database. This is the largest database of de-identified ALS clinical trial participants. The data is primarily from U.S. participants, many from NEALS clinical trials. This makes for an appropriate comparison, as the data is coming from a very similar source and context as CENTAUR, which is also run in the U.S. at NEALS trial sites.

The comparison groups for this analysis will once again be the observed AMX0035 ITT overall survival arms and a historical clinical trial control arm from the PRO-ACT database that has been propensity score matched to help account for selection bias.

In this analysis, participants in the PRO-ACT database were included in the control arm based on several criteria. They were control participants from historical trials; had a baseline and at least one post-baseline ALSFRS-R; met the major inclusion and exclusion criteria from CENTAUR at baseline; and had known mortality information, either known date of death or known alive at the end of follow-up. Propensity score matching takes these participants that are already a close comparison and matches them even further, based on known prognostic covariates to get a more apples-to-apples comparison. It's important to note that a statistical plan was prespecified prior to conducting the analysis.

A propensity score was calculated using key covariates that are known to be important prognostic factors for survival in ALS. These were time from symptom onset; ALSFRS-R pre-baseline slope; SVC or SVC at baseline; and age at baseline. A comparison of these baseline covariates are shown in the table. Generally, the groups were well

balanced. A Cox proportional hazards survival analysis was used to compare mortality of the observed ITT AMX0035 survival versus the propensity score matched historical clinical trial control arm.

As shown, the comparison to the historical clinical trial control arm demonstrates an 11-month median survival benefit for AMX0035 treatment. Hazard ratio was 0.48 in comparison to the ITT hazard ratio of 0.64. As before, we can also look at the visual for these results using the KM curve, again showing the median overall survival difference of 11 months.

The historical clinical trial control arm once again provides a treatment-naive comparator, allowing an estimate of the true survival treatment effect of AMX0035. In addition, it also uses propensity score matching, which is a methodology cited in the FDA's real-world evidence framework. Like the natural history prediction model, this analysis uses data from a new independent external control arm to the CENTAUR trial.

Again, the results seen with this different methodology are remarkably close to the first two methods, supporting the robustness of all three. Creating the control arm from the PRO-ACT clinical trial data base helps to address some of the limitations of the natural history prediction model, specifically that PRO-ACT is a clinical trial population, mostly U.S. sites, and many of these sites overlap with sites in CENTAUR. In addition, the ability to use propensity score matching on the PRO-ACT data set builds further confidence that the comparison groups are well matched.

In the context of the CENTAUR study, the ITT overall survival analysis on its own is confirmatory evidence of the benefit of AMX0035 beyond the benefit observed on the primary outcome, the ALSFRS-R. With more than 3 years of follow-up, treatment with AMX0035 demonstrated a robust, nominally significant, placebo-controlled ITT, overall survival benefit. These results are further supported by the new survival analyses with

different control groups that show an even greater survival benefit with AMX0035 when comparing to the ITT overall survival results. Despite different methodologies and data sources, each analysis found a similar outcome, namely a survival benefit of approximately 10 months for AMX0035 treatment.

Three independent treatment-naive control groups, including two that are external to the trial, all yield similar results: the crossover-adjusted placebo arm; external control number one, the natural history survival prediction control arm comparison; and external control number two, the historical clinical trial control arm comparison.

These three control arms use different sets of statistical assumptions, but all three result in the same outcome. No analysis method can do it all; that's why we chose each of these to provide additional information and address limitations. Collectively, these provide layers of support for the validity of the ITT overall survival result.

The CENTAUR study met its prespecified

primary outcome at 24 weeks. AMX0035 demonstrated a robust and clinically meaningful retention of function. Over greater than 3 years follow-up treatment with AMX0035 demonstrated a nominally significant ITT overall survival benefit. This benefit on its own merit is very meaningful in the context of a universally fatal disease such as ALS.

Comparing the AMX0035 overall survival results versus three new survival analyses with different treatment-naive control groups provide further evidence of benefit. Importantly, these three methodologies show concurrence in their estimates of overall survival. In summary, these results support AMX0035 meets the standard of substantial evidence of effectiveness.

I will now turn the presentation over to Dr. Cudkowicz to provide her clinical perspective on these results.

Applicant Presentation – Merit Cudkowicz

DR. CUDKOWICZ: Thank you. My name is Merit Cudkowicz. I'm the chief of neurology at Mass General Hospital, director of the Healey & AMG

Center for ALS and the Julieanne Dorn Professor of Neurology at Harvard Medical School. I served as the co-PI and senior clinical advisor for the CENTAUR study.

As a coordination center, Mass General received a grant from Amylyx. I did not receive any salary from that grant, nor have I received any personal consulting funds. I do not hold any equity in Amylyx, nor will I benefit from the outcome of this meeting, other than as a clinician who wants to provide better options for my patients, which is why I am here today.

I would like to share my perspective on the data and what this means for people living with ALS, the ALS field, and for clinicians who treat people with ALS. This is big for us, too. We have too few choices to offer our patients to slow this serious fatal disorder.

First and foremost, the CENTAUR study met its primary endpoint, showing a clinically meaningful and statistically significant 25 percent reduction in disease progression. This means that

my patients can maintain their function longer. We only have two approved drugs that impact clinical progression, riluzole and edaravone, and despite these, patients still face rapid progression and mortality. Given what is on the market today for ALS, this is a big step forward.

I have spoken to many of my colleagues that have reviewed the data. A large number of us want AMX0035 available for our patients now based on this data alone, and we have more data. AMX0035 importantly demonstrated about a 5-month survival benefit in the placebo-controlled ITT overall survival analysis. This analysis was robust, including all participants in CENTAUR. In addition to the ITT overall survival analysis in CENTAUR, we have presented new survival analyses that further support this benefit. All of these consistently show a larger survival benefit of about 10 months.

I was involved in the creation of the PRO-ACT database and have long collaborated with ENCALS. The presented survival differences compared to these well-curated data sets further

confirm the robustness in clinical meaningfulness of the findings to me. The results seen with the ITT overall survival analysis on its own is compelling in ALS, and the supportive analyses presented today indicate that the benefit is likely even greater. This approach to survival analysis is the future for ALS trials, and in my opinion, we need to be encouraging these approaches.

To that end, just a few weeks ago I was on an FDA-NINDS ALS Act webinar, where it was exciting to hear the initiatives around the importance of natural history databases and the desire to be innovative, have flexibility, and look at new ways to assess therapeutic benefit in ALS. It's also important to point out that a product that shows an effect like this would likely be approved on a single study in oncology.

ALS is just as serious and devastating as certain cancers. It's worse than others. In fact, the review in JAMA of all oncologic drugs approved between 2000 and 2016 showed a median 2.4-month overall survival benefit and a mean hazard ratio of

0.77. Using the most conservative approach, CENTAUR shows a 4.8-month benefit and a hazard ratio of 0.64. CENTAUR is the first and only trial to show a benefit on both function and survival, which is even more exciting given that ALS is an exceptionally challenging disease to study and measure in clinical studies.

I have personally been involved in 38 clinical trials for ALS. Of those, four had positive biomarker findings but did not meet their prespecified primary endpoint. Two met their primary endpoint, AMX0035 and Nuedexta, a asymptomatic ALS drug. Only one, AMX0035, showed positive results on both the primary functional results and survival.

I've also reviewed the concerns raised by the FDA on both the functional and survival benefit. The statistical comments have been fully addressed, and the study was designed with the best in the field and represents good ALS clinical trial design and execution. The benefit-risk balance here is clearly positive. AMX0035 slows

progression and extends life, and it's safe. The trial results and confirmatory evidence provide more than sufficient evidence to support approval.

It's easy for this conversation to become more abstract based on complex regulatory standards, but to me it's pretty simple. I see people living with ALS every day. I currently take care of 500 people living with ALS. I have cared for thousands in my career.

In my opinion, AMX0035 needs to be something that we can offer our patients now, not just an expanded access program that is limited in enrollment and eligibility, but for any appropriate patient in the United States. This is the right thing to do for people with a uniformly fatal, rapid illness like ALS.

To close, I'd like to revisit two time lines shared in this presentation to put this data and the question before you and perspectives. Our choices today very well may determine the lifespan of tens of thousands of people: the first time line shared by Tammy Sarnelli, showing that

the phase 3 study will complete in 2024, and if AMX0035 is not approved this year, an FDA decision will not happen until at least 2025, and the time line shared by my colleague, Dr. Paganoni, showing the diagnosis, progression, and death of a person with ALS in that same time frame.

This is not an extreme example. This is the norm; 5 [000] to 6000 people are diagnosed each year with ALS, and 5 [000] to 6000 people die each year with ALS. The choice today is not for people that will be diagnosed with ALS in three years; it's for the people currently living with ALS now.

Nobody said it better than Sandy Morris, a person with ALS and game-changing advocate who spoke at this last panel. Sadly, Sandy passed away last week. She urged us to take her baton and run faster and farther. ALS is all about time, and it's about time we pick up Sandy's baton and bring new promising therapies to people living with this disease today.

Thank you. I will now turn it back to Dr. Timmons who will take your questions.

Clarifying Questions to the Applicant

DR. MONTINE: Thank you.

We'll now take clarifying questions for Amylyx. Please use the raise-hand icon to indicate that you have a question, and remember to lower your hand by clicking the raise-hand icon again after you have asked your question. When acknowledged, please remember to state your name for the record before you speak and direct your question to a specific presenter, if you can. If you wish for a specific slide to be displayed, please let us know a slide number, if possible.

Finally, it would be helpful to acknowledge the end of your question with a thank you, and the end of your follow-up question with, "That is all for my questions," so we can move on to the next panel member.

I will call on people in the order that I see them, but it may not be the order that you raised your hand. So we'll begin with Dr. Nath.

DR. NATH: Hi. Yes, Avi Nath here. I have just three small, quick questions. One is for the

biostatistics group.

Were there any subgroups of individuals who may have responded better than others?

DR. TIMMONS: Yes. Thank you, Dr. Nath. This is Jamie Timmons. I'll be moderating Q&A.

If I heard the question correctly it's, is there any subgroup of participants who responded better than others?

DR. NATH: Yes.

DR. TIMMONS: There are a few ways to answer this question. We did, in the FDA briefing document, make mention of the responder analysis that was performed. There we looked to see, and we did see, a subgroup of participants who did show a response.

When we look at subgroups specifically in terms of concomitant medication use, baseline characteristics such as neurofilament, other disease characteristics, we are not seeing a clear difference in terms of subgroups. It's consistent across those subgroups.

DR. NATH: Alright. Thank you.

DR. TIMMONS: Great. No problem.

DR. NATH: The second question is probably also related to statistics, or maybe one of the clinicians could answer. And that is, it's interesting that the survival benefit changes depending on what kind of control group you use. The placebo group showed the 4.8 months, and then if you use the natural history study, you're looking at 9 or 11 months.

Why such a huge difference? It looks like the placebo group showed a survival benefit of several months if you compared it to the other natural history studies. Is it possible that in the CENTAUR study you're enrolling individuals who are slow progressors to begin with, and maybe that's why you happen to see the difference?

DR. TIMMONS: The critical difference in terms of the ITT overall survival analysis and the new survival analyses that we are showing today are that the new survival analyses are taking that placebo group treatment crossover into account. So that ITT overall survival analysis is a

conservative analysis for just comparing those two originally randomized groups. The new survival analyses are allowing us a comparison of a treatment-naive control group, which from our standpoint is what's explaining that difference, allowing us to see the real benefit from survival.

To answer the second part of your question in terms of did CENTAUR enroll either fast or slow progressing participants, we actually looked at this with that propensity score PRO-ACT arm, and what I'm showing here on the right, the PRO-ACT arm, this is the ALSFRS-R.

You can see here the progression rate of that PRO-ACT matched arm minus 1.69, aligning very closely to that placebo arm minus 1.66, and as a reminder, that PRO-ACT matched arm is matched to the AMX0035 group. So really, the key difference between those two groups is AMX0035 treatment leading to that benefit we see on the ALSFRS-R and the ITT overall survival analysis.

DR. NATH: The last question is the ALS Functional Rating Scale is largely dependent on

motor skills, but these patients often have a cognitive dysfunction as well, and there is overlap between that and FTD. So were any cognitive assessments done on this patient or they planned in the PHOENIX study?

DR. TIMMONS: In terms of the CENTAUR trial, we did not perform any specific cognitive evaluations. From a standpoint of inclusion/exclusion criteria, the CENTAUR trial did exclude participants who had unstable psychiatric disease, cognitive impairment, dementia, et cetera. In terms of the phase 3 PHOENIX trial, similar exclusion criteria there, but no specific assessments in the PHOENIX trial planned as well there, from a cognitive standpoint.

DR. NATH: Thank you.

DR. MONTINE: Thank you.

This is Tom Montine. Just as chairman's prerogative, we have about 10 minutes left for this session. Every committee member has their hand raised, so please try to be brief with your questions and your answers.

Next in line, Dr. Fischbeck.

DR. FISCHBECK: Thank you. Well, I have several questions. They are excellent presentations, by the way; several questions. I'll try to get in at least one or two of them.

One, the added analyses for this presentation included various statistical analysis methods. And I wonder if any of those were part of the original prospective analysis plan, and whether there were other analyses tried and found not to be supportive, and left out of the presentation.

DR. TIMMONS: Absolutely. To clarify, the new supportive analyses that we shared today, they were not part of the prospective prespecified plan, however, they are the only analyses that we did. Each analysis did have a plan that was created and finalized before the analysis was conducted, and we shared, as mentioned, to provide additional support to the ITT overall survival benefit.

DR. FISCHBECK: Okay.

Then second, there was a question that I had about use of historical controls. These are great

databases, but they go back to the 1990s. And there's a statement in the report that ALS survival and ALS outcome hasn't changed much since then, but I find that kind of surprising, particularly in comparison with other diseases like SMA and Duchenne dystrophy, where clearly there's been improvement in survival over the last 10-15 years before effective treatments have become available. And a lot of that is, I think, due to the hope that effective treatments will become available and more aggressive support, particularly ventilatory support, with non-invasive ventilatory support.

So I guess I wonder if that could be true, that these historical controls, particularly from the '90s, did worse than patients do nowadays and patients who were included in this study. And the way to get at that would be to limit the comparison to more recent data; say having a cutoff at 2000 or 2010; or the other question I had is whether the placebo arm of this study also did better than the historical controls.

DR. TIMMONS: Great. In terms of the

historical control question, I'll answer with some data points, and then Dr. Cudkowicz is going to share her clinical perspective. So to start from the data side, PRO-ACT is probably our best analysis to look at for this question. As mentioned, the original analysis that we showed in our briefing document and that we shared today is spanning a time frame from about 1999 to 2010.

Perhaps fortuitously, PRO-ACT just updated about two weeks ago, so we re-ran the same analysis that we showed you with that updated version of PRO-ACT, which would include more recent trials that include standard-of-care use of edaravone, et cetera. What we're seeing with that update is not a big difference in terms of survival. The original one I showed you was 11 months; here we're looking at 10.3 months.

Then bringing back up the slide that I shared earlier, where we are able to compare that PRO-ACT arm to the concurrent placebo control, again, that ALSFRS-R progression rate is quite similar.

I'll ask Dr. Cudkowicz to chime in quickly with our standard of care and her impressions there.

DR. CUDKOWICZ: Yes. I was going to make two points. One is that PRO-ACT is a great resource. And the really good news is that now every company who has benefited from being able to access that data for their work is agreeing to provide the placebo data afterwards. So it really did just get updated, and it's a huge resource.

Sadly, the disease course hasn't changed. The natural history hasn't changed in ALS, and we've looked at this, looking at placebo groups in past trials over the last decade, and that rate isn't changing, and Dr. Miller also in California has done the same. So again, it just goes back to the huge unmet need of the field to have treatments that will actually change survival and function.

DR. FISCHBECK: Yes, thanks. That's really helpful.

Just one quick other question, if I may.

DR. MONTINE: Sorry; if I may, because we're

going to run out of time. I don't mean to be rude. I'll cycle back if we have more time.

DR. FISCHBECK: Okay. Thanks.

DR. MONTINE: Dr. Robert Alexander?

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

I'd just like to focus again on this overall survival, and particularly the propensity score matching. It appears that if you had applied this method to the placebo group, you would also -- the group that started on placebo, you would have also found a survival benefit compared to the historical controls. So I just wonder if you could comment on that. Thank you.

DR. TIMMONS: In terms of the way that the PRO-ACT analysis was done, it was matched to the AMX0035 treatment group. What I do have here is the comparison of -- I'm sorry; I'm just bringing up the slide real quick here -- our treatment-naive subgroup, the placebo group, because, again, that 48 people who start on placebo, there are participants there who crossed over to receive AMX0035.

So to have a true treatment-naive placebo comparison, we need to look at the small subgroup of people who did not cross over. That's that gray line there. It's a small subgroup, granted, but we can see that that treatment-naive placebo group is aligning nicely to the PRO-ACT prediction.

DR. R. ALEXANDER: Thank you.

DR. MONTINE: Dr. Follmann?

DR. FOLLMANN: Yes. Thank you. This is Dean Follmann from NIH. I have two questions [indiscernible – audio breaks].

In the FDA briefing document, there is concern about the crossover-adjusted analysis. In terms of the crossovers that did take [indiscernible] -- placebo people who dropped out or didn't take drug [indiscernible] --

DR. TIMMONS: Sorry. I don't mean to interrupt, but we can't understand the question. I apologize.

DR. MONTINE: That's ok. We'll see if we can fix that in the background.

We'll move to Dr. Apostolova, please.

DR. APOSTOLOVA: Hi. I would like to look a little closer at the biomarkers, if you don't mind. These are slides 66 and 67. Arguably, the best biomarkers for ALS would be NfL, p-tau 181, and YKL-40. In terms of YKL-40, looking at slide 65-66, the units are comparable but the means look quite different. It's possibly because there is a lot YKL-40 in ALS, and I would love to hear your answer to that.

I wanted to know if there is 20 percent less YKL-40, and those from AMX0035, is that comparable to what is seen in Alzheimer's? Is the decrease comparable? Because what we see is a mean difference in the slide 66. And also, in terms of NfL, was it negatives in both the AD and the ALS analysis?

DR. TIMMONS: Yes. So to clarify a couple points there, neurofilament did not change in either the CENTAUR ALS study or the PEGASUS Alzheimer's disease study. Differences between the YKL-40 levels in Alzheimer's and ALS studies are a little tough because the Alzheimer's disease study

is CSF; the ALS study is plasma.

We do have Dr. Bowser on, who ran these analyses. I was having a little bit of trouble hearing you at the beginning, so if there was another question there, please feel free to repeat, and we can have Dr. Bowser weigh in as well, too.

DR. APOSTOLOVA: No, this was the question; if Dr. Bowser could clarify.

DR. TIMMONS: Okay.

(No response.)

DR. MONTINE: Thank you.

DR. TIMMONS: All set then?

DR. MONTINE: Yes.

DR. TIMMONS: Okay.

DR. MONTINE: I think we're at time. I apologize we didn't get to everyone, but there will be additional time when we come back for discussion and voting. So please keep your questions, and I apologize we weren't able to get to everyone.

We're now at a 15-minute break -- a 13-minute break. We will reconvene at 2:15 with FDA presentations. Thank you, everyone.

(Whereupon, at 2:03 p.m., a recess was taken.)

DR. MONTINE: Welcome back. We will now proceed with the FDA presentations, starting with Dr. Buracchio.

FDA Presentation – Teresa Buracchio

DR. BURACCHIO: Good afternoon. I'm Teresa Buracchio, director of the Division of Neurology 1, the division responsible for reviewing the new drug application, or NDA, for AMX0035 for the treatment of ALS. As you have heard from Dr. Dunn and the applicant today, we are reconvening the PCNS committee to continue discussion of this NDA in the context of additional analyses and data submitted by the applicant, in which the applicant has proposed to be considered as confirmatory evidence for this application.

The agency would also like this opportunity to provide further context to the committee regarding regulatory considerations for unmet need and regulatory flexibility in severely debilitating and life-threatening diseases such as ALS. The

agency recognizes the substantial unmet medical need in ALS, which also exists for many of the devastating neurological diseases for which treatments are so desperately needed. We feel that it is imperative that the committee is given the opportunity to consider this new information and whether it has the potential to contribute to the evidence required to support approval.

For today's presentation, I will provide a brief background, which will be followed by a discussion of the statistical considerations of the new analyses by Dr. Tristan Massie, our biometrics reviewer, and a discussion of the biomarker data by Dr. Emily Freilich, the cross-discipline team leader for this application. I will then conclude the agency's presentation with an overview of the regulatory considerations pertinent to this application to provide additional context for the committee discussions that will follow.

The applicant submitted an NDA for AMX0035 in October 2021. To support substantial evidence of effectiveness, the applicant submitted data from

a single double-blind, placebo-controlled phase 2 study, AMX0035, also known as CENTAUR, in 137 patients with ALS. The applicant reported a statistically significant result on the primary endpoint of the slope of the ALS Functional Rating Scale-Revised, or ALSFRS-R, at 24 weeks, with a 2.3 point difference from placebo at 24 weeks and a p-value of 0.034. The applicant also reported findings of the survival benefit from the open-label extension of CENTAUR in patients who initially received AMX0035 compared to those patients who originally received placebo in the CENTAUR study.

The committee met on March 30, 2022 to discuss whether the data submitted by the applicant is adequate to establish the effectiveness of AMX0035 in the treatment of ALS. At this meeting, FDA discussed analytical and interpretive issues for the consideration of the prespecified statistical results of the CENTAUR study and raised concerns with the overall persuasiveness and robustness of these results, given these issues.

Specifically, FDA noted the following issues: the randomization error and imbalances due to the initiation of background therapy edaravone during the course of the study; the statistical analysis methodology, which did not appropriately account for deaths that occurred during the study; and the appropriateness of the statistical assumption of linearity over time in the treatment effect.

FDA expressed concerns that the results from the CENTAUR study may not be capable of serving as a single study in isolation that provides substantial evidence of effectiveness; therefore, the study would need independent substantiation from either confirmatory evidence or another clinical trial.

Regarding the ability of the survival analysis from the open-label extension study to serve as confirmatory evidence, FDA noted concerns about the interpretability of the survival benefit, given the small study size and baseline imbalances in disease characteristics between the populations.

The committee was asked to vote on the following question. 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 ALS? Four members voted yes and six members voted no. There were no abstentions. Members of the committee expressed that the decision was difficult. Many of the committee members acknowledged that the ongoing larger phase 3 trial would help resolve the uncertainties regarding the effectiveness of AMX0035.

Following the advisory committee meeting, the applicant submitted additional analyses and data that it intended to contribute to the confirmatory evidence to support the primary result of the CENTAUR study. The survival analyses consisted of new analyses of the previously submitted survival data and contained no new data from the CENTAUR study or its open-label extension. The applicant also provided biomarker data from the

phase 2 Alzheimer's disease study as evidence of the effects of AMX0035 in another neurodegenerative disease.

I will now turn the presentation over to Dr. Tristan Massie from the statistical review team to discuss the new analyses of the survival data from the CENTAUR study and the open-label extension that were submitted by the applicant.

Dr. Massie?

FDA Presentation – Tristan Massie

DR. MASSIE: Thank you.

Good afternoon. I'm Tristan Massie, primary statistical reviewer for this new drug application for AMX0035, which I'll abbreviate as AMX, in ALS. Today, first I'm going to talk about a summary of the statistical analyses from the last meeting, followed by a discussion of the new analyses submitted after the initial advisory committee meeting.

At the March 30th advisory committee meeting, the statistical summary focused on CENTAUR, which was the single trial submitted to

establish effectiveness. The 2019 draft guidance for Substantial Evidence of Effectiveness states that, quote, "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," end quote.

There were some uncertainties about the results from the prespecified analyses of CENTAUR which were not highly persuasive for a single trial. There was more post-baseline use of edaravone and riluzole in the AMX arm. Additionally, deaths were not properly accounted for in the primary analysis. Furthermore, the assumption of linearity over time of the primary endpoint, ALSFRS-R, appeared questionable. Secondary endpoint results were not compelling, and survival analysis from time to death alone through the open-label extension were exploratory.

It is important to note that there is no new AMX data for ALSFRS-R or survival since the last

advisory committee meeting held on March 30th. The applicant has submitted new analyses based on previously analyzed CENTAUR data and some external data. There was no prespecified analysis plan for these analyses. They were planned and conducted after seeing the CENTAUR trial and CENTAUR open-label extension data. There are numerous analytical choices and assumptions for these analyses that affect the results, and lack of prespecification compromises the interpretability and reliability of these analysis results.

In the next couple of slides, I will talk about the new post hoc analyses. The first analysis is known as a Rank Preserving Structural Failure Time Model. This analysis models the survival of the placebo group in the counterfactual or hypothetical scenario in which they had not switched to AMX treatment in the open-label extension.

The placebo group completers of the double-blind period were eligible to cross over to AMX treatment by design of the open-label extension,

and 71 percent of the placebo group switched to AMX in the extension. Non-completers of the double-blind period were ineligible for open-label extension participation or treatment but were still included in the analysis.

The estimated hazard ratio for the RPSFTM analysis was smaller, but the precision is lower. The uncertainty is not represented in the survival plot as presented by the applicant. However, as seen in the table, the estimated hazard ratio -- the upper bound of the 95 percent confidence interval for the hazard ratio in the new analysis is essentially the same as in the survival analysis presented at the last meeting. It is on the border of a non-significant effect.

There are numerous issues with the new RPSFTM survival analysis. The RPSFTM is heavily dependent on non-testable assumptions. First, it is assumed that the survival time benefit is proportional to time on drug. Second, the exact same proportionality is assumed to apply to placebo after switching to AMX in the extension despite the

delay in the start of their AMX treatment and progression from baseline. RPSFTM models the hypothetical treatment-naive survival of the 71 percent of the placebo group that switched to AMX in the open-label extension.

Another concern with this analysis in this trial is the fact that placebo patients who switched to AMX are different than those who did not, but the model assumes they are the same. As evidenced in the difference, the mean baseline ALSFRS-R is 3.7 points higher for double-blind period placebo completers than for placebo dropouts, and the latter by study design were ineligible to switch to AMX.

A methodological reference article cited by the applicant indicates that the reported new survival analysis may be biased in favor of drug, and increasingly so as the proportion of placebo group switching to drug increases. The article states, quote, "We found that analyses which re-censored usually produced negative bias that is underestimating control group restricted mean

survival and overestimating the treatment effect," end quote. Further, it states that, "The increased switching proportion had an important impact, leading to increased bias, with the relative effect on the different adjustment methods dependent on the size of the treatment effect," end quote.

This switching proportion is quite high in this trial at 71 percent due to placebo completers switching to AMX by design of the open-label extension. The reference paper only studied lower switching proportions. The reference also recommended a complementary analysis in order to assess the bias. However, according to the applicant's reference article on CENTAUR analysis, quote, "Acceleration factor could not be estimated in assessments of on-treatment RPSFTM without applying the recensoring," end quote. Thus, bias of the reported RPSFTM analysis remains in question.

In addition to the RPSFTM analysis just discussed, the applicant conducted additional post hoc analyses. For the first of these

analyses, the applicant applied a survival prediction model developed by the European Network for the Cure of ALS, or ENCALS, to the CENTAUR AMX treatment group. This model was developed based on data from select European patients from 1992 to 2016. In the second analysis, the applicant used a post hoc propensity score matching model to select a subgroup from the external PRO-ACT database for a survival comparison to the CENTAUR AMX treatment group. This PRO-ACT database contains data from patients from ALS clinical trials from 1990 through 2010.

These are non-randomized comparisons to external data for which there was no common treatment protocol or prespecified analysis plan; therefore, patients in CENTAUR may differ from those in ENCALS and PRO-ACT cohorts. In particular, they may differ in measured prognostic factors, for example, stage or severity of disease. Furthermore, they may also differ in unmeasured prognostic factors. Additionally, patients in the external control, or population for model

development, may have received different supportive care and/or available therapies, yet another possible confounder of these post hoc non-randomized analyses.

The comparison to a PRO-ACT database subset relies on a propensity score matched analysis which involves numerous analysis choices, which were not prespecified. Only 74 of 89 CENTAUR patients randomized to AMX were matched, which may create bias. Both the ENCALS and PRO-ACT analyses were post hoc analyses only planned and conducted after having knowledge of unblinded CENTAUR trial data. Ideally, for these to be reliable, the analysis plans would have been in place before the conduct of the CENTAUR trial.

In summary, the new analyses of CENTAUR data do not provide a statistically persuasive effect on mortality. It is important to reiterate that there is no new AMX data since the last advisory committee meeting in March, only new analyses of the existing data from CENTAUR. There was no prespecified analysis plan for these new analyses.

They were planned and conducted after seeing the CENTAUR results and CENTAUR open-label extension results.

There are numerous analytical choices and assumptions that go into these analyses that affect the results, and lack of prespecification compromises interpretability and reliability of these analysis results. The unplanned analyses are exploratory and have limitations, as highlighted in this presentation.

Thank you. Now I'll turn it over to Dr. Freilich to continue the FDA presentation.

FDA Presentation – Emily Freilich

DR. FREILICH: Thank you.

My name is Dr. Emily Freilich, and I'm the cross-discipline team leader for this application. As part of the new material submitted, the applicant presents potential mechanistic evidence for an impact on neurodegeneration and neuroinflammation in CSF based on the summary of recent biomarker data collected in a related disease population. I will present an overview of

this data.

The applicant recently conducted PEGASUS, a phase 2 study in patients with clinical Alzheimer's disease or mild cognitive impairment. The randomized, double-blind, placebo-controlled study enrolled 95 patients, with 51 patients receiving AMX0035 and 44 patients receiving placebo. Patients were treated twice daily for 24 weeks. Approximately 80 percent of the AMX0035 patients and 96 percent of the placebo patients completed this study.

The primary objective of the study was to assess safety and tolerability of AMX0035 in the study population. No differences were seen between AMX0035 and placebo on the exploratory efficacy outcomes of cognition, function, or imaging measures, or on the prespecified composite outcome of all three measures. The study also assessed 18 CSF biomarkers on an exploratory basis that the applicant felt to be either core biomarkers for Alzheimer's disease or possible targets of the presumed mechanism of action of AMX0035.

The table shows mean change from baseline results of the exploratory biomarkers collected. According to the applicant, the biomarkers with nominally significant differences between the treatment arms were total tau; phosphorylated tau; neurogranin; YKL-40; fatty-acid binding protein 3; interleukin-15; 8-hydroxy 2 deoxyguanosine; and the beta amyloid 42/40 ratio.

The applicant has highlighted select markers, namely the lowering of CSF total tau, p-tau, neurogranin, and YKL-40, and the increased ratio of beta amyloid 42/40 ratio compared to placebo, as changes that may support the mechanistic activity of AMX0035 in the central nervous system. There was no change in neurofilament light, which is one of the commonly evaluated biomarkers of neuronal degeneration.

The reported changes may be suggestive of pharmacodynamic activity of AMX0035 in the central nervous system in patients with Alzheimer's disease. However, there is no clear or consistent relationship between the select biomarkers that did

have nominally significant changes and those that did not to suggest a true treatment effect of AMX0035 on either nervous system inflammation or neuronal degeneration.

It is difficult to draw any meaningful conclusions from the presented biomarker data. The underlying pathophysiology of Alzheimer's and ALS are different, as are the study populations, and the baseline levels of biomarkers may differ in these populations. Some of the biomarkers also may act differently in different disease states and stages of illness. Thus, any relevance of these findings to people living with ALS, even if they were demonstrated to indicate benefit in Alzheimer's disease, are unclear and not necessarily generalizable across neurodegenerative conditions.

Finally, we also note that the 18 biomarkers were assessed as exploratory endpoints and thus were not adjusted for multiplicity, and the interpretation of the p-value is limited. The submitted biomarker data are not clear evidence of

a potential for clinical benefit in patients with ALS.

I will now turn the presentation back to Dr. Buracchio to discuss the regulatory considerations.

FDA Presentation – Teresa Buracchio

DR. BURACCHIO: Thank you, Emily.

I will now discuss regulatory considerations for the evaluation of the data submitted for AMX0035 in ALS. This overview is intended to provide additional context for the discussions of the advisory committee that will follow.

To establish the effectiveness of a drug for approval, a legal standard for substantial evidence of effectiveness must be met. This standard applies to drugs for all diseases, from common, non-serious, and non-life-threatening conditions that have available therapies, to serious, life-threatening, and/or fatal diseases with few or no available therapies. This requirement was established in 1962 with the Kefauver-Harris Amendment to the Food, Drug, and Cosmetic Act that

included a provision requiring manufacturers of drug products to establish a drug's effectiveness by substantial evidence.

In this act, substantial evidence is defined as, quote, "evidence consisting of adequate and well-controlled investigations, including clinical investigations, by experts qualified by scientific training and experience to evaluate the effectiveness of the drug involved on the basis of which it could fairly and responsibly be concluded by such experts that the drug will have the effect it purports or is represented to have under the conditions of use prescribed, recommended, or suggested in the labeling or proposed labeling thereof."

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. Independent substantiation of a favorable result protects against the possibility that a chance occurrence in a single study would lead to an erroneous conclusion that a treatment is effective.

Although two adequate and well-controlled clinical investigations are the usual standard for generating substantial evidence of effectiveness in many diseases studied, there are scenarios in which a single trial can be used to establish effectiveness. The agency's ability to rely on a single study is further described in FDA's 2019 draft guidance, Demonstrating Substantial Evidence of Effectiveness for Human Drug and Biological Products.

This guidance states that reliance on a single 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 impracticable or unethical. In other words, we are able to rely on the evidence from the single trial in isolation when it provides evidence that is similarly persuasive to that which might result from two separate trials taken together.

Characteristics of a single adequate and well-controlled study that could make the study adequate alone to support the effectiveness of a product may include, but are not limited to, the following examples: a large multicenter study; consistency across study subsets such as age, gender, or disease stage; multiple studies within a single study such as a factorial design with multiple study arms; multiple endpoints involving different but related events; and statistically very persuasive findings.

As we discussed with the committee in March, the primary evidence provided by the placebo-controlled CENTAUR study is undoubtedly promising but does not appear to possess the characteristics that would allow it to serve as a

single study in isolation to establish substantial evidence of effectiveness; therefore, the study would need additional evidence to provide independent substantiation of the positive results.

Under certain circumstances, FDA can also conclude that one adequate and well-controlled clinical investigation of conventional persuasiveness, pus confirmatory evidence, is sufficient to establish effectiveness. In this situation, the confirmatory evidence would serve to provide independent substantiation of the results of the single study. I note that Amylyx is proposing to utilize this approach, with the CENTAUR study serving as the single adequate and well-controlled study and the survival analysis from the open-label extension study and the biomarker data from the Alzheimer's disease study proposed as confirmatory evidence.

Factors that FDA may consider when evaluating the appropriateness of this approach are described in the 2019 effectiveness guidance that I previously referenced, and include the degree of

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.

The guidance also provides examples of data or information that could potentially provide confirmatory evidence. These examples may include, but are not limited to, data from an adequate and well-controlled clinical study, or studies, to demonstrate the effectiveness of the drug in a closely related approved indication; data that provides strong mechanistic support of the drug in the pathophysiology; data from a well-documented natural history of the disease, and it is noted in the guidance that this may potentially be considered if it reinforces very persuasive and compelling results from a single adequate and well-controlled study; and scientific knowledge about the effectiveness of other drugs in the same

pharmacological class.

When substantial evidence of effectiveness is demonstrated by any of the situations I just described on a direct assessment of clinical benefit, this may result in a traditional approval. This is the usual approval pathway for most drug development programs.

Accelerated approval is a particular type of approval that FDA may grant for a product for a serious or life-threatening disease or condition upon a determination that the product has an effect on an endpoint that is not itself a direct measure of the clinical benefit of interest but is instead reasonably likely to predict the clinical benefit, taking into account the severity or rarity of the condition and the availability or lack of alternative treatments. Approval is subject to the requirement that the applicant study the drug further to verify and describe its clinical benefit.

It is crucial to recognize that the evidentiary standards for effectiveness are not

lower for endpoints used to support accelerated approval than for traditional approval. Substantial evidence of effectiveness on those endpoints must be demonstrated. Accelerated approval concerns the character of the endpoints, not the strength of the results on those endpoints. An effect on an endpoint supporting accelerated approval must be an effect on an endpoint that in its character is reasonably likely to predict clinical benefit and in its persuasiveness provides substantial evidence of effectiveness from adequate and well-controlled trials just as substantial evidence of effectiveness on a clinically meaningful endpoint from adequate and well-controlled trials supports traditional approval.

In the case of AMX0035 for ALS, the ALSFRS-R and survival are direct and clinically meaningful measures of benefit and are acceptable endpoints to support traditional approval. Therefore, if the agency determines that these endpoints met the substantial evidence requirements, we would be able

to grant a traditional approval.

I would also like to note that the agency does have withdrawal authorities if a drug is found to no longer meet the criteria for substantial evidence of effectiveness. It is commonly understood that under the Subpart H regulation, a drug that received accelerated approval may have its approval withdrawn if the drug's predicted benefit fails to be verified in a confirmatory trial. However, it is less commonly recognized that FDA does have authority under CFR 314.150 to withdraw approval of a drug if it finds, as stated in the regulation, quote, "upon the basis of new information for FDA with respect to the drug, evaluated together with the evidence available when the application was approved, that there is a lack of substantial evidence from adequate and well-controlled investigations, that the drug will have the effect it is purported or represented to have under the conditions of use prescribed, recommended, or suggested in its labeling," end quote. In other words, the evaluation of the

safety and effectiveness of a drug is a continuous regulatory process, and data may continue to accrue after an initial approval that called in question or negates a prior finding of substantial evidence of effectiveness. In this situation, the FDA has the authority to initiate withdrawal of approval procedures.

It is also worth noting that some other countries have marketing authorization pathways often referred to as conditional approval that allow for an approval of a drug that does not meet the evidentiary standards for effectiveness required for a full approval in those countries. This pathway may often be confused with the accelerated approval pathway in the U.S. regulations, however, there are distinct differences.

Both pathways are intended to expedite the availability of therapies that address an unmet need. Additionally, both pathways require subsequent confirmation of clinical benefit; however, the conditional approval pathway typically

allows for marketing authorization for products for which the benefit-risk of the medicine is positive. Unlike the accelerated approval pathway in the U.S., the conditional pathway does not have a requirement for a substantial evidence of effectiveness or its equivalent in that country; instead, these pathways typically rely on an overall assessment of the evidence.

In this regard, it is important for the committee and the stakeholders listening today to be aware of and note the recent approval of AMX0035 in Canada, using one of these conditional approval pathways under the Health Canada regulatory authority known as Notice of Compliance with Conditions.

This form of marketing authorization is granted to a product on the basis of promising evidence of clinical effectiveness. Promising clinical evidence is explained by Health Canada to be evidence based on well-controlled and well-conducted clinical trials, establishing that the drug product has an effect on a surrogate or

clinical endpoint that is reasonably likely to predict clinical benefit. It is similar in some ways to FDA's accelerated approval pathway, but relies on promising evidence rather than substantial evidence.

I will now discuss the regulatory concept of unmet medical need. Unmet medical need refers to a condition in which treatment is not addressed adequately by available therapy. ALS is a serious and devastating disease. There are currently three approved drug products in the U.S., riluzole and two formulations of edaravone. Although these drugs have demonstrated benefits for ALS, the disease often remains rapidly progressive and fatal despite these available therapies. The agency recognizes that there is an urgent unmet medical need for new treatments for individuals with ALS, and that this unmet need must be taken into account when considering the evidence supporting the AMX0035 application.

I will now turn to a discussion of the regulatory concept of regulatory flexibility. As

Dr. Dunn noted, our regulations allow for and encourage the use of regulatory flexibility to expedite the development, evaluation, and marketing of new therapies intended to treat persons with life-threatening and severely debilitating illnesses, especially where no satisfactory alternative therapy exists.

From CFR 312.80 Subpart H, I quote, "The Food and Drug Administration has determined that it is appropriate to exercise the broadest flexibility in applying the statutory standards while preserving appropriate guarantees for safety and effectiveness. These procedures reflect the recognition that physicians and patients are generally willing to accept greater risks or side effects from products that treat life-threatening and severely debilitating illnesses than they would accept from products that treat less serious illnesses. These procedures also reflect the recognition that the benefits of the drug need to be evaluated in the light of the severity of the disease being treated."

The 2019 Draft Effective Guidance also discusses the clinical circumstances where additional flexibility may be warranted, such as when a disease is rare or the disease is life-threatening or severely debilitating with an unmet medical needed. The guidance states that in certain settings, a somewhat greater risk of false positive conclusions, and therefore less certainty about effectiveness, may be acceptable when balanced against the risk of rejecting or delaying the marketing of an effective therapy for an unmet medical need.

The guidance also provides some example of the use of regulatory flexibility, such as consideration of alternate trial designs for the standard randomized, double-blind, placebo-controlled trial; the use of surrogate or intermediate clinical endpoints under the accelerated approval pathway.

In some situations, flexibility on the p-value can be considered. This would typically refer to a situation of a rare disease where the

sample size is limited. In those situations, a slightly higher p-value may be considered with appropriate justification and prespecification, and the number of trials considered sufficient to establish effectiveness such as in a rare disease where a second trial may be infeasible. In these cases, the substantial evidence of effectiveness would typically be provided by the situation we face today, which is a single trial plus confirmatory evidence.

There are three FDA-approved drug products for ALS, riluzole and the two formulations of edaravone. These approvals demonstrate the agency's history of regulatory flexibility in ALS. The approval of riluzole for the treatment of ALS was based on two adequate and well-controlled trials that assessed survival. In both studies, riluzole did not show a statistically significant difference using the prespecified statistical analysis method.

The agency felt that an alternative test was a more appropriate statistical analysis method for

these trials. Using this methodology, both studies were found to demonstrate nominally statistically significant effects on survival. The post hoc results from the two studies using the alternative statistical tests resulted in exploratory findings of nominal significance, and these were found to meet the substantial evidence of effectiveness standard for riluzole in ALS.

The initial approval of edaravone for the treatment of ALS was based on a single 6-month randomized, double-blind, placebo-controlled trial in 137 patients with ALS that was conducted exclusively in Japan. The study demonstrated a statistically significant difference of 2.5 points in decline on the ALSFRS-R with a p-value of .0013. The results were corroborated by multiple sensitivity analyses conducted by FDA. Results of several secondary endpoints trended favorably.

FDA noted that the study had characteristics that made it appropriate as a single study alone to provide substantial evidence of effectiveness. Some of these characteristics included a

multicenter study in which no single site contributed an unusually large fraction of the patients or was disproportionately responsible for the treatment effect; consistency across subsets of study participants; and persuasive results with strong p-values.

Although edaravone demonstrated a benefit on a functional scale, it is not known if edaravone has a benefit on survival in ALS. Although every drug development program is distinct and must be considered individually, this history of the application of regulatory flexibility in ALS provides relevant precedence when considering the evidence supporting the AMX0035 application.

As discussed at the prior advisory committee meeting, the applicant has an ongoing phase 3 study in ALS. Study A35-004, also referred to as PHOENIX, is a phase 3, randomized, placebo-controlled trial of AMX0035 in patients with ALS. The primary objective of the trial will be to assess AMX0035 compared to placebo on the change from baseline of the ALSFRS-R and survival

over 48 weeks. The study also includes a number of secondary endpoints relevant to ALS patients.

The study has planned to enroll approximately 600 participants at over 70 sites in the U.S. and Europe, and over half of these participants are enrolled at this time. The trial is expected to complete in late 2023 or early 2024 with results available shortly thereafter.

Undoubtedly, the results of the phase 3 study would be highly informative for a regulatory decision on the current FDA review for AMX0035, however, the results will not be available for another year and a half. This places the agency in a challenging situation of potentially making a regulatory decision that may not be subsequently confirmed by the results of the ongoing study.

If the agency does not approve the drug and the phase 3 study is positive, the approval of the potential effective drug will have been delayed. If the agency does approve the drug and the phase 3 study is negative, there will be a drug on the market for ALS which may no longer meet the

requirements for substantial evidence of effectiveness. However, the withdrawal authority that Dr. Dunn and I have previously described could be considered if it is found that substantial evidence of effectiveness for AMX0035 in ALS no longer exists.

I will now discuss the use of expanded access for AMX0035 in ALS. Expanded access, which is commonly referred to as compassionate use, is a potential pathway for patients with a serious or immediately life-threatening disease or condition to gain access to an investigation or medical product for treatment outside of clinical trials when no comparable or satisfactory alternative therapy options are available.

The applicant has initiated an expanded access program available in the United States, Study A35-006, to allow for access to AMX0035 for eligible adults with ALS. In order to enroll in a study, participants must have symptoms for at least 3 years and cannot be eligible to participate in clinical trials with AMX0035.

I will now conclude this presentation with a summary of where we find ourselves today in the review of this application. We have a single positive study. There are methodological and analytical concerns with the study that impact the persuasiveness of this positive finding, and these concerns were previously discussed at the March 30th advisory committee meeting, however, it is a positive study that won on its primary endpoint.

For consideration of confirmatory evidence, the applicant has conducted multiple post hoc exploratory analyses on the survival data from the CENTAUR study and its open-label extension that have shown a nominally positive benefit on survival. Although nominally positive, consideration of this data should note the potential for a study with a small sample size to be impacted by baseline imbalances in disease characteristics or severity.

The applicant also provided biomarker data from a phase 2 Alzheimer's disease study as

evidence of the effects of AMX0035 in another neurodegenerative disease. These data are interesting, however, the relevance of these observations in Alzheimer's disease to ALS is uncertain.

The applicant is conducting a phase 3 study in ALS that is currently ongoing and has completed approximately half of the planned enrollment to date. The trial is expected to read out in the next year and a half. This trial will provide additional information regarding the effectiveness of AMX0035 in ALS.

Finally, we must always consider in our regulatory deliberations that ALS is a serious and fatal disease with substantial unmet need; therefore, consideration of the application of regulatory flexibility is appropriate. As Dr. Dunn noted earlier today, substantial evidence of effectiveness is a qualitative, not a quantitative, standard that relies on the application of scientific judgment to consider the evidence in the context of disease severity and unmet need.

Regulatory flexibility is a fundamental aspect of our general regulatory framework, and it must inform our considerations of the data before us.

With this background in mind, we are seeking the committee's advice. We ask you to consider the complexities of this situation in your discussion. We ask the committee to discuss the strength of the currently available data regarding the effectiveness of sodium phenylbutyrate/taurursodiol to include the new information submitted and the information presented in the March 30, 2022 PCNS meeting. The discussion may include considerations regarding the unmet need in ALS, the status of the ongoing phase 3 trial, and the seriousness of ALS.

We are asking the committee to vote on the following question.

Considering the new information submitted, along with the information presented at the March 30, 2022 PCNS meeting, is the available evidence of effectiveness sufficient to support approval of sodium phenylbutyrate/taurursodiol for the treatment of patients with ALS? In addition to

the prior and new evidence presented, you may take into account in your vote the unmet need in ALS, the status of the ongoing phase 3 study, and the seriousness of ALS. Thank you.

Clarifying Questions to the FDA

DR. MONTINE: Thank you.

We will now take clarifying questions for the FDA. Please use the raise-hand icon to indicate that you have a question, and remember to lower your hand by clicking the raise-hand icon again after you've asked your question. I can see some of you are doing this already. Great.

When acknowledged, please remember to state your name for the record before you speak and direct your question to a specific presenter if you can. If you wish for a specific slide to be shown, please let us know the slide number, if possible. Finally, it would be helpful to acknowledge the end of your question with a thank you or the end of your follow-up with, "That's all for my questions," so that we can move on to the next panel member.

I will, I think, modify how we did this from

the last time. I'd ask each person that I call on, each panel member, to ask one question. We'll move to the next panel member. If you have multiple questions and you've raised your hand again, we'll cycle back.

Okay. So we'll begin. The first panel member on my list, Dr. Traynor, would you please ask your first question?

DR. TRAYNOR: Hello. Can you hear me?

DR. MONTINE: Yes, I can.

DR. TRAYNOR: Yes. Hi. This is Bryan Traynor here. I guess I'm directing this question to FDA; perhaps Dr. Dunn in particular because he had specifically raised this issue.

I noted that the CEO of the company had said that they would voluntarily withdraw the drug if the subsequent phase 3 trial turns out to be negative, and I commend them in that. However, I think we all know that pharmaceutical companies change ownership and change CEOs quite frequently, so I'd like to ask Dr. Dunn, what are the actual procedures in place for the FDA to withdraw the

approval for the drug, which would not be a voluntary withdrawal, but actually a forced one?

Has that ever happened before? Is it something that would take years to accomplish or is it something that is just relatively straightforward and can be accomplished at an administrator level? Thank you.

DR. DUNN: Dr. Traynor, this is Dr. Dunn. Thank you for your question. I understand it, and I want to make sure that we're not conflating two different things because both I and Dr. Buracchio, I think, attempted to address this in our presentations.

The comment by the CEO of the company at today's meeting is not something that is a substitute or a replacement in any way for what we discussed with you, which was our regulatory authority to withdraw approval of the drugs, so those two things are distinct and unrelated in that manner.

Dr. Buracchio and I both covered the same information, and in the interest of efficiency we

won't repeat that here, but the agency does have formal regulatory authority to withdraw approval of a marketed drug. There's a procedure for that. I think it would be misrepresenting things to suggest to you that it's -- I forget what words you just used, but something along the lines of is it straightforward, simple, easy.

I think we all know, folks working in government, that things take some time. The procedure is there. It is often viewed as a complicated path to pursue. I think that's a fair way to put it; however, it is there. It's important that we're aware of it, and we wanted the committee to be aware of it.

It's a fairly straightforward regulation, but of course the application of it requires notices of opportunities for hearings and notifying the sponsor. And the various maneuvers have to be gone through to accomplish that, but it is something that the agency is prepared to exercise when the circumstances call for it.

DR. MONTINE: Thank you, Dr. Dunn.

Next, Dr. Nath, please, your question?

DR. NATH: Yes. My question is, again, related to Dr. Buracchio. You'd discussed the false positive and false negative risks, but what about the possibility that if the drug were to be approved, then enrollment in the placebo arm of the PHOENIX study may be compromised.

Is that a concern at all?

DR. BURACCHIO: Hi. This is Dr. Buracchio. We have discussed this with the sponsor in the past. My understanding, and perhaps they can confirm, is that enrollment in the U.S. for the PEGASUS trial -- for the PEGASUS or PHOENIX maybe -- PHOENIX trial has stopped. So should the drug be approved in the U.S., I think that all of the U.S. participants would have already completed the trial, although the trial is still ongoing in other countries.

Perhaps there's someone from Amylyx who can confirm what I've just said.

DR. TIMMONS: Yes. Hello, Dr. Buracchio. This is Jamie Timmons from Amylyx. I can confirm

that enrollment in the U.S. is no longer under way for the PHOENIX trial. The PHOENIX trial is largely a European trial. The majority of sites are in Europe, and as mentioned, U.S. approval would not impact European completion of the study.

DR. NATH: Great. Thank you.

DR. MONTINE: Thank you all.

Dr. Caleb Alexander, please, your question?

DR. C. ALEXANDER: Yes. Can you hear me?

DR. MONTINE: I can.

DR. C. ALEXANDER: Great. This is Caleb Alexander. I guess, first, just a comment or two.

Dr. Dunn, I would be interested -- I'm not clear if there have been instances where the FDA has actually forced the manufacturer to withdraw products -- that was part of the last question, and I didn't hear that -- but I do think that the history of accelerated approvals and the ability of the FDA to force manufacturers to fulfill the commitments that have been made prior to approval provide some context to consider that particular matter.

You know, we're being asked here to consider a natural -- we're not being asked to consider the natural history studies as confirmatory but rather the open-label analyses, and this evidence isn't from a separate study; it's from the same study as the pivotal trial. So I just have two questions regarding this. I know I can just ask one now.

I know that these studies -- I understand that the open-label analyses were post hoc and performed after unblinding with no evidence of statistically significant effects on death or the composite in the double-blind phase, but I wondered -- and I guess this is a question for Tristan Massie -- whether there was evidence of a correlation between the duration of drug exposure and survival in CENTAUR that would provide some further confidence about this exposure outcome relationship.

DR. MASSIE: Hi. This is --

DR. BURACCHIO: Sorry. I wasn't sure. There were two different questions in there. One was for Dr. Dunn regarding further consideration of

the withdraw authority.

Dr. Dunn, did you want to address that?

DR. C. ALEXANDER: Yes. I was told I could just ask one, so I guess I was making a vast of comments, but I'd be happy to hear from Dr. Dunn as well. But the main question is for Dr. Massie pertaining to whether or not there was a relationship between duration of drug exposure and survival in the CENTAUR study.

DR. BURACCHIO: Dr. Massie?

DR. MASSIE: Hi. This is Tristan Massie. There weren't any prespecified analyses to assess whether there was a relationship between exposure and survival. I think the sponsor presented a table showing different groups of placebo dropouts and placebo completers, but the problem with that is that they're not groups; they're at random. So they're not representative of the full placebo group; so that table doesn't really answer the question.

DR. MONTINE: Thank you. And I would ask the panel members, after you've asked your question

if you would lower your hand just so we can keep track of who's on deck.

Next is Dr. Robert Alexander.

DR. R. ALEXANDER: Thank you, Dr. Montine. It's Robert Alexander.

My question to FDA is that it seems like the primary objection to these additional survival analyses was that they weren't prespecified. So if they had been prespecified, is this a type of analysis that you would consider confirmatory evidence even though it's from the same trial? Thank you.

DR. BURACCHIO: Dr. Massie, would you like to start on that or see if we need to add more?

DR. MASSIE: Hi. Tristan Massie. The problem, even if this analysis has been prespecified, I think the Rank Preserving Structural Failure Time Model, to my knowledge -- and I talked with oncology statisticians -- to my knowledge, it's not used for regulatory decision making even in oncology.

So it has such strong assumptions, but I'm

not sure that -- have helped it

(Crosstalk.)

DR. R. ALEXANDER: I was referring to the comparison to the natural history cohort.

DR. MASSIE: Well, the same issue there. It wasn't prespecified, and you have the problem of they still might not be comparable because there could be unmeasured prognostic factors. There's no randomization to assure that you're comparing balanced groups.

DR. R. ALEXANDER: So just to be clear, are there any circumstances where that type of analysis could be considered confirmatory?

DR. BURACCHIO: Hi. This is Dr. Buracchio. I think it would be hard to say right now. Such an analysis is a really complicated analysis, and I think we would generally recommend that if there is a plan for such an analysis, that it be discussed with the agency prior to initiating that trial so that we can see if we can come to any agreement on the criteria used for matching and the analysis procedures that are planned.

So I can't say that, no, we wouldn't ever accept something like that for confirmatory evidence, but I think it really is important to have some sort of an agreement with the agency on that approach before conducting the study in order to agree to it generally.

DR. MONTINE: Thank you.

Dr. Fischbeck, please?

DR. FISCHBECK: Yes. This is Dr. Fischbeck. Again, I have several questions, but maybe just to ask a follow-on question to that of Dr. Nath about what will happen with the phase 3 study if there's FDA approval here, I'd like to ask the other way around.

If there is no approval here, if the decision is negative by the FDA, based on CENTAUR, is there a chance that PHOENIX enrollment, which ended in March 2022, whether that would be restarted if the decision is negative? Which would answer some of the patients and family member requests for access to this drug; at least it would be good to have access through the clinical trial.

DR. BURACCHIO: I'd have to turn that question over to Amylyx to see if they've given that any consideration.

DR. FISCHBECK: Yes, maybe Dr. Sarnelli.

DR. TIMMONS: This is Jamie Timmons. I can answer that question --

DR. FISCHBECK: Sure.

DR. TIMMONS: -- on behalf -- the study is recruiting well. We're over 370 participants now. As mentioned, it's a largely European study. It's needed for EMA approval. It's also, as discussed, part of the conditional approval for Canada. Should the AMX0035 not be approved in the U.S., we'll of course evaluate, but the plan currently is not that we would need to reopen sites in the U.S.

I'll ask Dr. Cudkowicz to provide her thoughts here, too, as well, just given I know this has been a discussion in the community.

DR. CUDKOWICZ: I'll just say briefly that there is a commitment from this company to complete this phase 3 trial with or without this requirement from Canada, and I'm very impressed by that. It is

enrolling well. The sites are activated in Europe. We are going to eventually get the second study, but it is going to be mid-2024 and, again, I think that's too late.

I think the people in the study in the U.S., the participants, they are committed to that trial. They're enrolling in that study to help others, and that's altruistic, and I'm thankful for them. And I'm confident that we're going to get a very good phase 3 trial, but it's going to be too late for people living today with ALS.

DR. FISCHBECK: Thanks.

DR. MONTINE: Thank you.

Dr. Apostolova?

DR. APOSTOLOVA: Hi. My question would be to the drug company, Dr. Paganoni most likely. Can we please briefly review the side effects from this therapy if we're discussing potentially marketing a drug that could be later withdrawn from the market if the large trials are not successful?

If I remember correctly, there are not very significant side effects. Can we review those,

please?

DR. TIMMONS: Just getting off mute there. Yes, this is Dr. Timmons from Amylyx. I'd be happy to do so. Pulling up here is -- I think we'll bring up a slide, if we can, bringing up the safety slide from the study in just one moment. I'll talk while we're waiting for that.

What we saw in the CENTAUR study is that adverse events were similar between the AMX0035 and the placebo arm. Almost everyone in the study did have an adverse event, mostly secondary to ALS disease progression. What we do see is that there were more severe adverse events in the placebo arm by a few percentage points compared to AMX0035.

When we kind of dig a little bit deeper into the safety data, the real difference between AMX0035 and placebo in this study was that there was a higher incidence of GI adverse events, so diarrhea typically in the first 3 weeks, but then would often get better; some abdominal pain; nausea.

I'll ask Dr. Paganoni, who has participated

in both the CENTAUR trial and the PHOENIX, to see if there's anything further to add there.

DR. PAGANONI: Hi. This is Dr. Paganoni. I agree with what Dr. Timmons said. Overall, there was a similar rate of adverse events between active and placebo. However, we did see in a small group of participants that they were more gastrointestinal side effects, as Dr. Timmons described, specifically nausea, abdominal pain, or diarrhea.

I would want to emphasize that this was only in a small subset of participants that most occurred during the first 3 weeks, so right after initiation of treatment, and then they subsided. So in the grand scheme of things, when you think about the fatal nature of the disease and the rapidly progressing nature of the disease, these were adverse events that were mild, manageable, and transient. So again, I don't think there would be a concern from the point of view of the prescribing physician. Thank you.

DR. MONTINE: Mr. Weston, please?

MR. WESTON: Thank you. I have a number of questions. Some of them can wait until later. My question is probably mostly directed at Dr. Buracchio, and it's sort of contextual, so I'll try to phrase it.

First, I want to comment that I'm finding this meeting today exceedingly frustrating. The FDA, as I understand it, re-invited the drug sponsor, the applicant, to come back and do this again, similar to the March 30th meeting; but, really, the stress has been on the fact that there's no new information -- rather, no new data -- and the analysis continues to be badly flawed from the perspective of the FDA. So that's why I'm frustrated by this.

My question is, why did the FDA refer the invitation to the applicant to go through this again if -- and I'm not saying you guys have made a decision, I know that's not done yet, but there's not a lot of positive discussion about the results of this new analysis of the old data. It almost feels like this is a setup to say, gee, we warned

you, we know we're going to approve the drug, but we have to go through these motions.

Could you please comment on that?

DR. BURACCHIO: Right. I can assure you that this isn't just something to go through the motions. At the time that the applicant first made us aware of these new analyses that they had run and published -- so these were also published and were in the public domain -- we are able to see the top-line results of these, but we are not able, at that point, to dig into the analysis and really critically appraise them.

So all we could say is, well, those sound interesting, potentially promising; we will review those. You may submit them, and we will review them and consider them as part of your application. It is only during the formal review process, after receiving them and looking through them, that we are then able to really thoroughly and critically go through them, and come up with our critiques and questions about them.

So at the time that we accepted those

submissions and extended the advisory committee meeting, everything is done on good faith; that these are promising analyses that should be considered and are worth considering. I think we note the limitations of the analyses, but we still haven't taken it off the table that they could be considered as confirmatory evidence, and that's why we're here today.

I don't know if Dr. Dunn or anyone else would like to add anything to what I've just said.

(No response.)

DR. MONTINE: Well, thank you. Thank you for the question. Thank you for your answer, Dr. Buracchio.

I believe everyone who raised their hand -- oh, excuse me. Did I interrupt someone?

(No response.)

DR. MONTINE: I believe everyone who raised their hand has had an opportunity to ask one question. There are still some hands up, so I'm just going to try to do a second round. Please be brief. We have four hands raised.

Dr. Follmann, do you have an additional question?

DR. FOLLMANN: Yes, thanks. Actually, I had the question that Dr. Nath raised, and I'd like to ask a question of the sponsor from the original go-round, if that's ok.

DR. MONTINE: Well, if we could, we'll have time for additional questions for the sponsor. If we could try to focus on questions for the FDA in this session, that'd be great.

DR. FOLLMANN: Yes. I don't have a question for the FDA. Thanks.

DR. MONTINE: Okay. Thanks, but we'll come back to you later.

Dr. Caleb Alexander, do you have additional questions for our colleagues at the FDA?

DR. C. ALEXANDER: I do. I have a question for Dr. Massie, and I want to say I appreciate the concerns regarding the new analyses insofar as they are post hoc; and as you identify, analytic choices and assumptions, many of them can affect the results of these analyses.

But I want to go back, if we can, to the open-label analyses of death. I know that they were post hoc. I know they weren't prespecified. I understand that the applicant pivoted to those after unblinding and after the composite outcome was examined but, Dr. Massie, can you share data, or at least explain a little bit further your concerns about the interpretability of the primary open-label mortality analyses where death was collected from 136 of 137 participants, and where there were analyses performed that were an intention-to-treat?

DR. MASSIE: Hi. This is Tristan Massie. The main concern is first, survival or time to death alone was not the key endpoint, so there is a multiplicity issue. And then there was a lot of lack of participation in the open-label extension, so we're not sure about concomitant medications and lost to follow-up.

DR. C. ALEXANDER: Thank you.

DR. MASSIE: And the final result for a single study, it's borderline. It's not

statistically very persuasive.

DR. MONTINE: Thank you, Dr. Massie.

DR. MASSIE: Right. Thank you.

DR. MONTINE: Thank you both.

Dr. Dayno, do you have a question for the FDA?

DR. DAYNO: Yes. This is Jeff Dayno, and just a quick follow-up from the previous question for Dr. Massie.

I think, based on some of the natural history data for the analysis of overall survival, and recognizing -- I think as Dr. Alexander just spoke to -- that those analyses were post hoc, I think in the spirit of regulatory flexibility, given the importance of natural history data, especially in diseases like ALS, as well as the recognition of natural history data in the FDA's framework for using real-world evidence, the question in the PRO-ACT, the analysis from PRO-ACT, or propensity score matching, doesn't that address some of the concerns, your concerns, about imbalance in the treatment group from that specific

analysis using that natural history data for overall survival? Thank you.

DR. BURACCHIO: Is that for Dr. Massie?

DR. DAYNO: Yes, that was for Dr. Massie.

DR. MASSIE: Sorry. I was on double-mute.

It could help a little bit, the propensity score, but the problem is it needs to be prespecified. There are many choices you can make in which variables to match on, and even if you do that, there could be unmeasured prognostic factors, so it will never attain the level of a randomized comparison. And there's also the constancy issue that patients in the database may have been seen a long time ago, and there could be a lack of comparability based on that.

DR. DAYNO: Thank you.

DR. MONTINE: Dr. Fischbeck.

DR. FISCHBECK: Yes. This is Dr. Fischbeck. I have a couple of more substantive questions for the company that maybe we can get to later, but just a minor point of clarification, and maybe I just missed this.

In the briefing document from the FDA, there's some discussion of responder analysis but I didn't see that in the Amylyx briefing document or that have come up today, and I was wondering what happened to the responder analysis. And then the other is, what does the abbreviation AWC stand for? It's not on the list of abbreviations, but it's in the briefing document and also on one of the slides.

DR. BURACCHIO: This is Dr. Buracchio. I'll just note that I apologize for not having the AWC in the abbreviations, but that just means adequate and well-controlled study.

DR. FISCHBECK: Oh, okay.

DR. BURACCHIO: Okay. I think I can turn it over to Amylyx to answer your other question, though.

DR. FISCHBECK: About the responder analysis?

DR. BURACCHIO: Yes, about the responder analysis. We had it in the FDA presentation. I'm not sure why Amylyx didn't include it in their

presentation.

DR. TIMMONS: Yes. Hello. This is Jamie Timmons from Amylyx; happy to answer that.

While the responder analysis does provide some additional support to the primary outcome, we chose to focus our briefing document and today's presentation on the confirmatory evidence, which for us is the ITT overall survival data plus the new three survival analyses. So it's really just a decision to kind of focus our discussions and make sure that that the ITT overall survival analysis was fully understood, and that we had enough time to really go through the methodology for each of these three new analyses.

DR. FISCHBECK: Okay. Thanks.

Open Public Hearing

DR. MONTINE: That's great. Thank you both. I think we'll now move on to the open public hearing session.

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 products, and if known, its direct competitors. For example, the 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 on 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 for this open public hearing be conducted in a fair and open way, where every participant is listened to carefully and treated with dignity, courtesy, and respect. Therefore, please speak only when recognized by the chairperson. Thank you for your cooperation.

We're now ready to proceed. Speaker number 1, your audio is connected now. Will speaker number 1 begin and introduce yourself? Please state your name and any organization you are representing for the record.

(No response.)

DR. MONTINE: Perhaps we will return.

(No response.)

DR. MONTINE: Perhaps we'll return to speaker number 1.

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

DR. HEIMAN-PATTERSON: Thank you very much for this opportunity to talk for a few minutes. My name is Terry Heiman-Patterson, and I direct the MDA/ALS Center of Hope at Temple University. I participated in numerous clinical trials, including the CENTAUR and PHOENIX trials with AMX0035, and that is my conflict, that I have participated in those trials.

I come to you today wearing two hats. First, I am a clinician who has cared for people living with ALS for more than 40 years. I remember a time when all I could do was provide symptomatic care, and there were no trials. However, despite all the progress and many more trials, we still have only two agents, one with two formulations that have been approved and that have a modest effect on survival and the functional change. The disease remains relentless with an unchanged

natural history, as pointed out by Dr. Cudkowicz.

The second hat I wear is as a clinical scientist who's actively involved in trials, as well as clinical research to understand and provide better care for people with ALS. In this role, despite the excitement of all the ongoing trials in the hope for the future, I do believe we cannot have false hope or costly drugs that are not effective. However, I also know that we do not need to have a home run for a drug to be worth approving.

I would like to advocate for AMX0035 as a promising therapeutic agent. The CENTAUR trial demonstrated decreased functional decline as measured by the validated ALSFRS-R score. Further, when examining the data from the entirety of the study, including the open-label portions, there was a clear survival benefit and an increased time to the first hospitalization and tracheotomy. This has already been presented.

The survival for people with ALS on the drug for both the trial and the open-label extension was

anywhere between 6.9 and 10.6 months longer than those on placebo first, who then went on drug, and 18.8 months longer than those folks who were on placebo and chose not to go on open label. Further, the survival has been increased over historical placebo groups from other data sets. This is a promising and robust result, and not a trivial amount of life when we consider that the average life is 34 to 36 months and quoted as 3 to 5 years.

I hope that the FDA and advisory committee will consider the nature of this cruel disease and the increasing amount of evidence supporting the efficacy of AMX0035 that's been presented when they consider the drug for approval. I am confident that with wider use and real-world evidence, the effect on disease will be borne out, and when I wear my clinician hat, I'll be able to give pals more options and promise. Thank you.

DR. MONTINE: Thank you.

Speaker number 3, your audio is now connected. Will you please begin and introduce

yourself? Please also state your name and any organization you are representing for the record.

DR. WOODS: Hi. William G. Woods. I represent myself. I also refer you to my written testimony, which was published in STAT a couple weeks ago. I have been an acting pediatric oncologist for 45 years.

The differences between the oncology center and the neurosciences center at the FDA are incredibly striking. I show a slide, which you've never seen before, that has to do with the overall survival of childhood leukemia in patients who enrolled in NCI-sponsored clinical trials from 1968 to 2009. You can see these 10 curves, a steady improvement in overall survival.

How did we do this? One trial, not two; not a confirmatory trial, one trial randomized, gold standard versus the gold standard plus an additional drug or a different approach to the drugs, and often that was the superior arm, and that became the gold standard for the next trial, and so forth. We currently have a 5-year survival

of 90 percent.

Many of you probably have children. Imagine if we had to do a confirmatory trial, we would be 20 to 25 points lower right now than we are. I know you would want the best chance for cure in kids. We have top-drawer, world-class biostatisticians who are sympathetic to the human condition, which is the most complex organism on earth.

How has the oncology center of the FDA done what they've done? They've understood novel drugs and not afraid of accelerated approval, and they have approved some drugs, single arm, with a 3-month survival. They've used intermediate endpoints, and frankly the ALSFRS-R is a great intermediate endpoint.

Studies show that out of 82 trials listed for accelerated approval in the last decade, two-thirds for cancer, only one brushed on a neuro disease. It was muscular dystrophy. What is wrong with that picture? The overall survival for the drugs that we currently have is in the range of

3 months. The side effects of the AMX0035 are temporary diarrhea. The phase 3 trial is ongoing. If it shows no benefit, take the drug off the market, but in the meantime, you can help save countless lives. With all due respect, the neurosciences office has been incredibly slow and behind the curve in using tools available to increase access of drugs to patients who need them. [Inaudible – audio lost].

(Pause.)

DR. MONTINE: Excuse me. I was on mute.

Can we please move on to speaker number 5?

DR. HEITZMAN: My name is Daragh Heitzman. Thank you for allowing me to speak. Regarding disclosures, I've given presentations for pharmaceutical companies, including Amylyx, in the past, but I'm speaking on my own behalf.

I'm a neurologist in private practice in Dallas, Texas, part of a large single specialty neurology group called Texas Neurology. Although I've practiced general neurology, my focus is neuromuscular disease; in particular ALS. I

founded our ALS center two decades ago, which is sponsored by both the MDA and ALSA to provide care to these patients and offer research opportunities.

Our ALS center is now one of the largest clinics in the country, and research has been a significant component of our ALS center. I've been involved in clinical research since the early 1990s, participating in almost 60 trials, mostly pertaining to ALS. At the moment, riluzole is the only approved medication that has been shown to improve survival, although nominally.

The disappointments and frustrations experienced by the ALS community have been immense regarding recurrent failed trials. I've been a participant in the CENTAUR trial and currently participating in the PHOENIX trial. Because the window to treat and demonstrate the efficacy of an experimental drug in the setting of ALS is short -- related to, one, the rapid progression of disease and significantly reduced life expectancy, which is approximately 2 years from the time of diagnosis; and two, the small numbers of patients

affected -- trial designs have had to adapt to take into account this small window of opportunity similar to oncology trial methodology.

One of the methods incorporated into the CENTAUR analysis was the Rank Preserved Structural Failure Time Model discussed in the literature, which demonstrated efficacy of sodium phenylbutyrate/taurursodiol. The Amylyx briefing document also includes a statistical analysis from ENCALS natural history of PRO-ACT databases that reiterate a positive response to PB-TURSO and the evidence of central neurologic effects of PB-TURSO in the Alzheimer's population.

In summary, the CENTAUR trial was a significant achievement, demonstrating that PB-TURSO provided three positive outcomes: 1) a significantly slower rate of decline of the ALS Functional Rating Scale, over 6 months, which correlates with a greater preservation of function; 2) a delay in first hospitalization; and 3) most importantly, prolonged survival. I strongly encourage, as do my ALS colleagues, that you

approve sodium phenylbutyrate/taurursodiol for this fatal disease, ALS, and feel that the evidence supporting its efficacy is strong. Time is too short for these patients and families. Thank you very much.

DR. MONTINE: Thank you.

We're going to go back to speaker number 4. I apologize.

Speaker number 4, thank you for your patience. You would think after 2 and a half years, I'd know how to do Zooms, but I was muted, begging you to please speak. So speaker number 4, would you please introduce yourself? State your name and any organization that you represent for the record.

DR. MAISER: Thank you. Good afternoon. I have no financial conflicts of interests. If you could please show the slide that I submitted.

My name is Sam Maiser. I'm a neurologist that specializes in ALS and palliative medicine from Hennepin Healthcare in Minneapolis, Minnesota. I'm an ALS researcher and the site PI for the

CENTAUR trial and the ongoing PHOENIX trial, but primarily a bedside clinician. I'm speaking today on behalf of all people affected by ALS. I'm asking the FDA to approve AMX0035 for ALS patients now. Please do not make us wait for the completion of a phase 3 trial.

My testimony today will follow three themes: efficacy, safety, and time. Per the FDA, a single study could justify approval if the disease is serious, fatal, and inadequately treated, and the findings of the study were robust and substantial. ALS is all of those things, and CENTAUR was substantial, robust, and rigorous.

It was a 24-week study with 137 people, multisite, and the validated primary endpoint was met, showing a decline or 25 percent reduction in the rate of progression of the ALSFRS-R, and the open-label extension showed people were living 5 to 6-plus months longer; 5 to 6 months longer is huge in the world of ALS. This is meaningful to them on a day-to-day basis. I rely on good science to provide the best care for my patients, and I'm

confident that these results are substantial and demonstrate efficacy.

Let's turn to safety. Safety is very important to me as a clinician and researcher, and I know it's very important to the FDA. The combination of agents is safe. The adverse events were mild, and all of my patients tolerated them well. One is a supplement available for years, and the other one is already FDA approved for other reasons. So given the low risk of AMX0035 and the efficacy of the drug as demonstrated in CENTAUR, approving AMX0035 is both scientifically and clinically a supported decision. It's the right decision.

Let's turn to time. Time is everything in ALS. My patients right now do not have time to wait another 2 to 3 years for the PHOENIX trial to be done, analyzed, and potentially approved by the FDA. Most of my patients will be dead by then. The ALS community needs your help. To deny them access now will mean that people with ALS will continue to decline and die at a rapid rate and

that CENTAUR has been supported by PHOENIX, that we'll have denied people living with ALS the possibility of a better life for a little longer. But if you allow them access now and CENTAUR is proven wrong by PHOENIX, then my patients will have been taking a safe drug that ended up not being helpful. But if CENTAUR is supported by PHOENIX, then people living with ALS right now, today, will be living better for a little longer.

As an ALS neurologist that specializes in palliative care, this is huge. The CENTAUR trial has convinced me it will do this for my patients. I urge you to trust the science, trust the specialists, trust the patients, and please approve AMX0035 now. Thank you for everything you do for this country, and I'm grateful to have had this time with you. Thank you.

DR. MONTINE: Thank you.

We'll move now to speaker number 6. Your audio is connected. Will you please begin by introducing yourself? State your name and any organization you represent for the record.

DR. GWATHMEY: Hello. I'm Dr. Kelly Gwathmey, and I am a neuromuscular neurologist and the ALS clinic director at Virginia Commonwealth University in Richmond, Virginia. I would like to thank the FDA advisory committee for this opportunity to speak in support of AMX0035 for ALS. I'm the site principal investigator for the phase 3 PHOENIX trial and the expanded access program, in which we currently have 5 patients receiving AMX0035.

The following statement reflects my own personal views, and I have received no personal compensation for this testimony. I have no pertinent financial disclosures, though have participated in consulting for myasthenia gravis pharmaceutical companies, not ALS pharmaceutical companies.

AMX0035 has a novel mechanism of action involving amelioration of endoplasmic reticulum and mitochondrial stress, ultimately resulting in reduced neuronal cell death. This represents a new approach to the treatment of ALS. Riluzole is

purported to modulate glutaminergic transmission, albeit it likely has a more complex effect, and edaravone likely reduces oxidative stress. AMX0035 is distinctly positioned to target several suspected pathogenic disease mechanisms from a unique and likely synergistic angle.

As we move closer to a cocktail approach to managing this disease, it is becoming increasingly clear that utilizing a single pharmaceutical with a sole drug target is an insufficient and ineffective approach. As a clinician with approximately 175 ALS patients, one of the largest cohorts in my state, I find the evidence for survival benefit to be particularly compelling. AMX0035 conferred a 9.7 to 11-month survival benefit in CENTAUR when methods accounting for crossover from placebo to AMX0035 were utilized.

Compared to riluzole trial data, suggesting a survival benefit of 2 to 3 months, albeit, it could be as long as 6 to 19 months based on real-world data, and edaravone for which we do not have robust survival data, AMX0035 results from

CENTAUR are extremely promising and clinically meaningful. As with any new pharmaceutical, providers must weigh the potential risk and benefits of the drug to the patient while also considering other therapeutic options.

Considering that VCU is a site for the expanded access program with 5 patients currently on AMX0035, I can speak to the drug's tolerability, as well as ease of administration. In keeping with phase 2 data, some patients have had mild gastrointestinal side effects, but the majority tolerate AMX0035 very well. This is a small price to pay for a drug that can slow progression of disease, extend life, and lower the risk of permanent ventilation and hospitalization. AMX0035 should be integrated into our current ALS treatment paradigm. Thank you very much for your time and attention.

DR. MONTINE: Thank you.

Speaker number 7, your audio is now connected. Will you please begin by introducing yourself? State your name and any organization you

represent for the record.

DR. WYMER: Yes. My name is James Wymer, and I am the chief of neuromuscular disease and a professor of neurology at the University of Florida in Gainesville, Florida. I am the director of the ALS Multidisciplinary Clinic and the Gainesville VA multidisciplinary ALS clinic, where we follow, between both institutions, 250 to about 300 patients with ALS.

I have been a site principal investigator in both the CENTAUR as well as the PHOENIX study, and I am also involved in the expanded access as well as the compassionate use program. I have received some funding for the research, but otherwise have not received any compensation for my time, and I am not on the Amylyx Speakers Bureau or any other compensation have I received from them.

I would like to start by thanking you for letting me speak in regards and in favor to the AMX0035, but what I want to talk about is -- well, two parts; one about the disease, as well as the second section where I focus on the science and

what we see. Rather than talking about the disease and how devastating it is with a survival of about two years, I would like to emphasize some of what others have emphasized, and that is the amazing spirit we see in our ALS patients.

We see these patients a year or 18 months into their symptoms, where they have just a few more years to live, and during this time, we witness their gradual decline. We see patients that are just losing motor function in front of our eyes, but they still have this fight to do everything they can to fight the disease. They are there with us. They are trying to improve quality of life as much as they can, and they see us as clinicians not because they want a drug to cure them; they want us to get in there and to help them so they can continue to live quality of life and live longer.

They see me for both pharmacologic and non-pharmacologic interventions to try and improve their function. Any medication that has the potential to increase the survival for 5 to

10 months is something that will have a profound impact on these patients, and based on AMX0035, it has the potential by delaying this devastating disease and providing quality of life.

As a researcher, I am always interested in medications that are based on sound science, and we have had years of medications that worked in cell and animal models but failed in clinical trials. With the introduction of AMX0035, as was mentioned, we have a combination therapy that is working on multiple pathways rather than one single pathway. You have the PEGASUS data that shows it is having an impact on biomarkers, and then the CENTAUR data with clinical data to show it slowed decline and prolonged survival.

AMX0035 --

DR. MONTINE: Excuse me, speaker 7. We appreciate your comments, but your time has elapsed. Would you please conclude?

DR. WYMER: Okay. Yes, that's where I was. Thank you.

DR. MONTINE: Sure.

DR. WYMER: AMX0035 clearly has impact on disease, is well tolerated, and delaying approval will limit its use to a generation of patients, limiting their quality of life. Thank you.

DR. MONTINE: Thank you.

Speaker number 8, your audio is now connected. Will you begin and introduce yourself? Please state your name and any organization you represent for the record.

MR. BURGHARD: My name is Vance Burghard. I was diagnosed with ALS in December of 2017. I've been a participant in the CENTAUR clinical trial, 2018. I am not being compensated in any way for my testimony.

At the time of my diagnosis in 2017, I was experiencing extreme weakness in my arms, as well as my hand-grip strength. Dressing was extremely difficult. I needed assistance to pull up my pants. Zipping them required help or assisted tools. I could not get my arms up high enough to put a T-shirt on by myself. Walking had become extremely difficult. I had required a wheelchair

to get to my appointment throughout the Mayo Clinic. I was fitted at that time for a brace to help address my foot drop. I had to stop working at my store, as I no longer had the strength or stamina to stock shelves or help customers.

Upon my return home, I was put on prescriptions of riluzole and Radicava. I was asked by my neurologist at Oregon Health and Science University if I'd be interested in participating in a clinical trial for AMX0035, which I began in March of 2018. My first strength test found my grip strength in my hands to be 18 pounds and leg strength extremely low.

I began to notice a change in strength and mobility by June of 2018. My wife and I began to travel again, and I no longer needed a wheelchair to get around airports, although I was still using a brace. By the end of the year, in 2018, I was again able to work, overseeing the daily operation -- [inaudible - audio break].

This drug has greatly improved my quality of life and that of my wife, children, and

grandchildren. I walked many miles during Europe, China, and Tibet. Three years ago, I would never have thought this to be possible. My health and strength seem to have stabilized. At my last ALS clinic, my neurologist stated there has been no change in my condition for the last three years.

AMX0035 for me has been a life-changing drug, and I ask that you quickly [inaudible] -- for the treatment of ALS so that others affected with this disease can benefit from it. Thank you.

DR. MONTINE: Thank you.

Speaker number 9, your audio is now connected. Will you begin by introducing yourself? And please state your name and any organization you are representing for the record.

(No response.)

DR. MONTINE: There you are.

Pardon me, speaker number 9?

DR. PATTEE: Can you hear me?

DR. MONTINE: I can. Thank you.

DR. PATTEE: Once again, I currently serve as the MDA medical director for the adult

neuromuscular clinic at the University of Nebraska and have been involved in clinical ALS trial research for over 30 years. Our research site was initially involved in the very early development of dexpramipexole, identifying its potentially beneficial effect in ALS. Throughout my career, very few investigational drugs have shown promise for ALS patients, and work with and experience with AMX0035, whose drug compound targets both the endoplasmic reticulum and mitochondria, suggests that this may be one of those drugs.

Our site has been involved in several ALS studies, including the Amylyx CENTAUR trial, the open-label extension trial, and recently the ongoing PHOENIX trial. We also have many patients in the expanded access Amylyx program, all of which have tolerated the medication well without significant side effects reported, and have remained committed to this drug trial.

The CENTAUR study results did reveal a reduced rate of decline of the ALSFRS-R over 6 months, with a preliminary projected analysis

suggesting prolonged survival, which is very compelling and which is rarely reported with this disease process. The hypothesis that both the endoplasmic reticulum and mitochondria play a critical role in the pathogenesis of ALS has also been well established in ALS literature.

The rationale for ALS treatments to date has focused on a combination therapy approach. We currently have FDA approval of riluzole and Radicava, which presumably targets the cytotoxic and anti-inflammatory pathogenic mechanisms, to the addition of another therapeutic agent possessing a dual mechanism of disease progression both pharmacologically and clinically. This would only complement the combination therapy approach even further.

Given the positive data from the CENTAUR study, determination of early approval for AMX0035 should be strongly considered. The clinical rationale of providing the earliest medical treatments at the earliest stages of ALS may improve the efficacy of these drugs through their

use and their modification on the influence of the disease progression, and approval of this drug until ongoing confirmatory study results have been completed appears to be clinically appropriate. Now, should these studies establish continued efficacy, the FDA has provided a potentially life-changing therapeutic option within this interim time frame.

In conclusion, it would therefore be my clinical recommendation that this drug should be considered for FDA approval at this time. By integrating AMX0035 as an option for inclusion in the current disease treatment regimens, this may lead to a significantly positive overall impact on the patients we care for, including the entire ALS community which struggles daily to cope with the effects of this devastating disease. I wish to thank you for your time and consideration.

DR. MONTINE: Thank you very much.

Speaker number 10, your audio is now connected. Will speaker number 10 begin and introduce yourself? Please state your name and any

organization you represent for the record.

MR. CANTER: Thank you. My name is Gregory Canter, and I have no affiliation with Amylyx. Back in 2014, many of us participated in the ALS Ice Bucket Challenge. Probably many of you listening to this meeting participated. I certainly did with my family. At the time, it was a game to me because it didn't affect me. I didn't have ALS. I didn't know anybody who had ALS; therefore, it didn't make sense to me. At the time, I didn't understand the impact that ALS plays on a single person, nor their family. Four years later, it all hit home when I was diagnosed.

I'm going to get straight to the point. I want the FDA to approve Amylyx. I'm not saying you should approve it because I think or I hope it works; I'm asking you to approve it because I know it works. It is extending my life, and I want that for others.

In January 2019, I entered the Amylyx trial. It was a 6-month trial that ended June 2019. I entered the trial with a 60 percent FVC or

respiratory capacity. At the end of the 6-month placebo-controlled phase, I had dropped all the way down to 44 percent. While I do not know for certain, I believe I was on the placebo arm. I say that because of what happened next.

In July 2019, I entered the open-label extension, and here I am; 3 years and 2 months later I am still alive, living independently, and my disease progression has significantly decreased. Some examples include I'm not terribly short of breath; my oxygen level is good, roughly 95 to 96 percent; I'm not close to that 25 to 30 percent range of going into respiratory failure; and the rate of my functional decline before Amylyx has slowed considerably since being on the drug. That's significant effectiveness, and Amylyx and its ingredients, Turso and sodium phenylbutyrate, have already showed themselves safe.

I look at ALS like this. I'm in a house with a basement and a ground floor, separated by a flight of stairs. ALS is the basement. Amylyx can start us up the stairs. They won't take us to the

top alone, but each step up is important and going in the right direction, and that's what we need. Without Amylyx, we're all still stuck in the basement. Thank you.

DR. MONTINE: Thank you.

Speaker 11, your audio is now connected. Will you please introduce yourself? State your name and any organization you represent for the record.

MS. PETERSEN: I would like to thank the FDA and the advisory committee for giving me the opportunity to share my perspective. I have consulted for several pharma companies and the ALS, including Amylyx, but I am not being compensated in any way by Amylyx for this testimony.

My name is Gwen Petersen. I testified before you in March as a person living with ALS. I shared with you that I was diagnosed at 32, no family history, no genetic mutations found. I told you that if I can get ALS, anyone can get ALS. One thing about me is different now. I decided to try AMX0035 after the March meeting. At that meeting,

I was persuaded by the extended rate of survival, slower disease progression, and the safety. profile.

I want to help you understand why I made my informed decision to go into the AMX EAP. I let the science lead: one, other ALS drugs have less data; two, the safety profile is good. I know all too well what side effects are like. I know what pain is. I've had 10 lumbar punctures as part of another study for ALS. The benefit-to-risk ratio for AMX for me is far more benefit than risk. While I've been on AMX for too short of a time to measure disease progression, I've had no side effects at all, not even diarrhea like some have reported.

Furthermore, this is the most low-maintenance, experimental therapy I've been on. We're talking about a drug, and it doesn't impact when I can have my morning coffee and eat my breakfast, unlike other oral drugs for ALS. I would love for AMX0035 to be a permanent fixture in my medication regimen, and with the FDA's

help -- this is really important -- grow the ALS cocktail to further slow down disease progression. Thank you.

DR. MONTINE: Thank you.

Speaker number 12, your audio is now connected. Will you please introduce yourself, stating your name for the record and any organization you represent?

DR. LADHA: Thank you for allowing me to speak today. My name is Shafeeq Ladha, and I direct the Gregory Fulton ALS Center at Barrow Neurologic Institute, where I not only care for a large number of ALS patients but I also conduct most of our clinical ALS studies. I would like to comment on the AMX0035 FDA application, and I'm doing so on my own behalf.

As a disclosure, I have served on advisory boards for Amylyx and have been an investigator for their clinical trials, but otherwise I have no financial interest in the outcome of the advisory committee's decision.

As someone who has spent most of his career

taking care of persons with ALS, I continue to feel the emotional toll of what the disease does to people and families. As one of the cruelest diseases, I don't need to convince anyone that there is still an urgent and unmet need for ALS treatments. AMX0035 has the potential to add to our ALS armamentarium. I'd like to briefly outline why I've come to this conclusion.

First, despite the approval of riluzole and edaravone, there is still clearly an unmet need. For those on the committee not involved with ALS care, you would be touched and motivated by the length persons with ALS are willing to go for the hope of treatments.

Is it truly better not to approve AMX0035 because of what I see as fairly minor criticisms in the clinical development program, and instead have persons with ALS traveling to other countries for completely unproven, costly, and risky treatments? This is exactly what is happening, and will continue to happen if we cannot provide them with more therapies.

Next, I think the analyses performed by the applicant are actually quite convincing. While the FDA comments rightly conclude that the new analyses are not independent assessments of the drug's effectiveness, I find it compelling that the data set analyzed in multiple ways actually reached the same conclusion. To me, that reinforces strongly the possibility that there is a true effect.

Finally, I feel that we are unlikely to find drugs in the near future that are highly effective on their own. Cocktails of drugs that target different disease, causing mechanisms to cumulatively have a robust effect of slowing disease progression, is the best approach currently.

Isn't it just as effective to use five drugs that each slow the disease by 10 percent as it is to use one drug that slows it by 50 percent? And it is much more likely that we will find the five drugs before we find the one with the dramatic effect. Exercising regulatory flexibility to approve drugs with perhaps smaller effects will

more easily allow us to add agents to this drug cocktail to give persons with ALS more hope and quality days to their lives.

I realize that this committee and the FDA cannot be swayed simply by emotion and public sentiment, but in this case I believe that there is enough positive data in the AMX0035 trial program, that when combined with an understanding of the journey a person with ALS must endure, and a little compassion, approval of this drug is warranted. I respectfully thank you for your time and attention.

DR. MONTINE: Thank you.

Speaker 13, your audio is now connected. Will you please begin by introducing yourself? State your name for the record and any organization you are representing.

MR. KOWALSKI: My name is Steve Kowalski, and I have no conflict of interest to disclose, and I'm not representing an organization. I am 58 years old, and I was diagnosed with sporadic ALS in 2017. Since 2017, I have seen an increase in funding for ALS research. Conversely, what I don't

see is the same progress in ALS drug development coming to market. Simply put, our medical needs are not being met.

The FDA 2019 ALS guidance continues to be tested with this submission of AMX0035, particularly in exercising regulatory flexibility. AMX0035 shows 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.

Considering the new information submitted and the information presented back in March, is the evidence of effectiveness sufficient to support approval given the unmet need and seriousness of ALS? I say it is. AMX0035 met its primary endpoint in trial. Additional data provided by the sponsor shows an extension of life, and it shows a slowing in the decline of function.

Last time I came before you in March, I asked you to consider the human value, h-value,

along with the p-value shown in clinical trials. Any additional time with loved ones or maintaining physical function has measurable value on the quality of life and self-independence. More time and function is valuable to every human being. We know what ALS looks like. I live every day with its devastating physical effects.

Once again, I'll 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 quick. Either way it ends in the same exact way, with one final breath. We cannot wait years for the PHOENIX trial when people with ALS are looking at a treatment that is safe and effective today. If we wait, many who are living with ALS will no longer be with us.

I want to take a moment to honor those ALS patients who passed during their participation in the CENTAUR trial and those that have passed since March who advocated alongside me in this effort. Their sacrifice is heroic. I will continue to advocate for accessibility of treatments in honor

of them and with every breath I have.

In a world increasingly defined by wins and losses, regulatory flexibility versus substantial evidence of effectiveness is a complex judgment analysis. If there's true flexibility in the FDA regulatory approval process, the time is now to recommend the approval of Amylyx 35 as an example that it's just not possible, but in fact an ongoing practice. Thank you for your time.

DR. MONTINE: Thank you.

Speaker 14, your audio is now connected. Will you begin by introducing yourself? State your name and any organization you represent for the record.

MR. KAUFFMAN: Good afternoon. My name is Scott Kauffman, and I'm the volunteer chair of the ALS Association Board of Trustees, and I have no personal conflicts of interest to disclose. The ALS Association was an early grant funder of AMX0035, and those grants included a standard payback provision capped at 150 percent of our grant. Any funds received as part of this

provision will be used to fund new research to find treatments and cures for ALS. We also fund the PRO-ACT database.

My son Steven was diagnosed with ALS 10 years ago when he was just 27, and as a parent, I can assure you that it's the worst possible diagnosis you can hear about your child. Some of you have already heard my story. It's the same one I told the FDA in 2021 at the We Can't Wait Action Meeting, calling for quick action on AMX0035. It's the same one I told this committee in March. The only thing that's changed since then is the number of months lost waiting for access to a drug we know to be safe and effective.

The new data submitted by the sponsor and the urgent need for new tools in the ALS toolkit show that there's plenty of evidence to say AMX0035 is a viable treatment for people living with ALS today. The association makes our recommendation based on important considerations of safety and clinical benefits.

First, results from the phase 2 trial

clearly show that AMX0035 is safe and effective for people living with ALS. Second, after just 6 months of treatment, AMX0035 significantly slowed ALS functional progression by 25 percent according to the rating scale used by physicians and researchers. Data also showed that the earlier you got started on AMX0035, the better the outcomes were on survival. And third, new data analyses and two separate publications have shown AMX0035 can have substantial effects on the long-term survival of those living with ALS, an increase of 10 months over those who received the placebo, and the complications associated with ALS were reduced by half. AMX0035 represents a meaningful step forward in progress. Ten months is a long time for someone living with ALS.

Now, I'm going to skip the rest of my remarks and speak directly to what we've heard here today, which has been remarkable. We heard the FDA indicate support for regulatory flexibility in this case, particularly if the sponsor would agree to remove the product if the PHOENIX trial is not

successful, and we immediately heard the sponsor agree to remove the drug from the market in that case. This is exactly the sort of creative problem solving we need from pharma and the FDA if we're going to find treatments and cures to this horrific disease. So I want to thank both the FDA and Amylyx for their flexibility, their creativity, and their commitment to finding solutions.

I strongly urge you to recognize the great unmet need in this space and the willingness of the FDA and Amylyx to be flexible. People living with ALS don't have time to spare. Please, make the right decision and determine there is sufficient evidence about the safety and efficacy of AMX0035 to make it a treatment option for people living with ALS today. Thank you.

DR. MONTINE: Thank you.

Speaker number 15, your audio is now connected. Will speaker 15 please introduce yourself? Please state your name and any organization you represent for the record.

MS. THOMPSON: Good afternoon. My name is

Christa Thompson. For the record, I am not being compensated in any way. I'm not affiliated with any organization, nor do I have any conflicts of interest. My husband Olin was diagnosed with sporadic 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 compassionate extended-use program. I'm here to testify that this treatment slowed Olin's progression and gave us at least 10 more months with him.

I want you to know that AMX0035 prolongs life and increases quality of life. Olin took it with no side effects for over 2 and a half years. While it was devastating to watch my love and the father of our three sons lose function week after week, he kept his smile, his ability to use his communications device, and the ability to enjoy our family until his death on July 18th. He was also able to stay in the extended-use study. ALS kills quickly, so we must have treatments that keep people functioning so that they can participate in

future clinical trials. Extending life and slowing progression means more moments with each other.

When I testified in March, we were talking about getting 6 and a half more months; now we are talking about getting at least 10 more months. What does 10 more months of function mean to our family? Well, it means that Olin was able to go out to dinner a week before he died and enjoying ice cream with his sons. It means Olin never lost his sweet smile or his love for vanilla ice cream. In the past 10 months, Olin got to see our oldest finish his first year of college.

Over the past 10 months, Olin enjoyed creating a fish tank for us to have after he was gone. I say good morning and good night to our fish every day. Towards the end of his life, Olin asked that we read him his favorite book. We all took turns reading to him. The night before he died, my 12 year old sat by Olin's bedside and read aloud to his dad. Ten months ago, I don't think my then 11 year old could have done that.

If you hear nothing from me today, please

hear this. Those ten additional months mean that Olin's youngest son knows that he read to and comforted his dad in his final hours. It means we get to share the fish tank, the smiles, and an ice cream. AMX0035 helped us keep our irreplaceable Olin for at least 10 more months. We got more moments and more time to be a family of five. Please do not rob other families of those 10 months. Address the unmet need for ALS treatments and recommend AMX0035 for full approval by the FDA, because when you only have memories left, 10 more months of making memories means everything. Thank you so much for your service and for the opportunity to speak today.

DR. MONTINE: Thank you.

Speaker number 16, your audio is now connected. Will you begin by introducing yourself? Please state your name and any organization you represent for the record.

MS. BACKMAN: Good afternoon. My name is Andrea Pauls Backman. I'm the CEO of the Les Turner ALS Foundation. My only disclosure is that

the Les Turner ALS Foundation received less than 2 percent of all annual revenues from pharmaceutical companies, including Amylyx Pharmaceuticals.

Since 1977, it has been our mission to advance scientific research for the prevention, treatment, and cure of ALS, and to provide the most comprehensive care and support to people living with ALS and their families so they can confidently navigate this disease. I want to add our perspective on what access to AMX0035 would mean to the people we serve.

Meet our support services team. We take an individualized approach to ensure each person living with this disease receives the very best quality of care. We visit them in their homes, we meet with them as clinic, and we check in by phone and video. We treat each person we serve like family, and every year we lose about one-third of them to this terrible disease. Let me introduce you to a few of the people we've lost since the last advisory committee in March.

Mary Ann Batterman-Daeschler was a mother of four, step-mother of five, and a grandmother of 19. When we talk about a treatment that can add 10 to 18 months to a person's life, we're also talking about more time that 19 children could have with a grandmother they loved. Some will go through life with clear memories of their Nana; some will only know the pain of absence. All of them will feel that loss for decades to come.

Michael Snedden loved cooking for big crowds because it was a way to bring friends and family together and show his love for them. His epic tailgates became a successful catering business because he enjoyed providing delicious food for the most important event in people's lives. ALS robbed him of the ability to cook for others, and it eventually took away his own ability to eat. A treatment that could have slowed his decline of function by as much as 25 percent would have meant the world to him and to his loved ones.

This is Kathleen Friend. Like Mary Ann and Michael, she is survived by a large and loving

family. She loved Christmas, puzzles, and music. In every way, Kathy was larger than life, but ALS confined her within her body. Before she died, she told her family that when she dreamed, she was running free. Today should have been her 73rd birthday.

There is an urgent and unmet need for safe and effective therapies for ALS. On average, people live 2 to 5 years following an ALS diagnosis. Imagine what 10 to 18 more months would mean to them. Imagine what it would mean to slow the loss of their dignity and independence by as much as 25 percent, and spend that much more time sharing the memories and experiences that make life worth living.

On behalf of the people we serve, on behalf of the people we've lost to this disease and the loved ones they've left behind, we urge the FDA advisory committee to recommend full approval of AMX0035. We have no time to waste. Thank you.

DR. MONTINE: Thank you.

Speaker number 17, your audio is now

connected. Please introduce yourself, stating your name and any organization you represent for the record.

DR. ANDREWS: My name is Dr. Jinsy Andrews, and I'm the director of neuromuscular clinical trials at Columbia University. I've been caring for people living with ALS and conducting clinical trials in ALS for over 15 years. I serve as the current co-chair of the Northeast ALS Clinical Trial Consortium and a volunteer trustee for the ALS Association, and work part-time at the James J. Peters VA hospital.

My comments today reflect my own personal views and not of the organizations that I'm affiliated with. I have consulted with several sponsors developing drugs for ALS, including Amylyx, although I was not an investigator for the CENTAUR clinical trial. I am an investigator for the PHOENIX trial that's ongoing and involved in the expanded access program. I do not have equity in Amylyx, and I'm not compensated for my participation today.

As an ALS specialist in the field, I wanted to provide the strength and context of the data from the CENTAUR trial. As you heard, the CENTAUR study was an adequately designed, randomized, placebo-controlled trial. It was designed in collaboration with experts in the field and people living with ALS, using methods commonly employed in ALS clinical trials and accepted by the ALS community. The study was conducted at top ALS clinical trial centers across the U.S.

I won't belabor the outcome measure of ALS Functional Rating Scale and survival. As you hear, it's very deeply meaningful from not only a clinical perspective, but from the ALS community perspective. But it's important to note that these benefits were noted on top of standard of care, and although this is certainly not a cure for ALS, people living with ALS have shared numerous times that anything that is safe and has potential to preserve function and extend survival is valuable and meaningful to them.

It's also important to note that although

CENTAUR was not powered on secondary endpoints, it showed a strong trend toward protecting pulmonary function, which is a predictor of survival in ALS, and had a statistically significant impact on upper extremity strength, in addition to having an effect on a patient-reported outcome called the ALS Assessment Questionnaire. Just to provide context here, prior to CENTAUR, we have not seen a phase 2 clinical trial hit on its prespecified outcome measure of the ALS Functional Rating Scale and show consistency in survival, other measures of function, and a patient-reported outcome.

I would also like to note that people newly diagnosed with ALS in the U.S. will not have a chance currently to participate in the clinical trial, as enrollment is closed and the EAP has very limited slots and may not be accessible to the thousands with ALS that are not clinical trial eligible today.

Making decisions about potential treatments for serious life-threatening diseases like ALS is never easy, and I'm very grateful to our colleagues

on the panel for deliberating this and the agency for having a second discussion. Waiting two to three years for results of a second study is essentially a death sentence for people living with ALS, and as a clinician, there's no debate about the safety of AMX. I think the worst case scenario was presented earlier, which is rejecting or delaying the marketing of an effective therapy; that should PHOENIX be positive, we would have delayed access to a treatment that would have made living longer and better for people living with ALS today. The agency has acknowledged flexibility in their approval process, and I urge them to use it in the case of AMX0035. Thank you.

DR. MONTINE: Thank you.

Speaker 18, your audio is now connected. Will you please begin by introducing yourself, stating your name and any organization you represent for the record?

MR. MELMEYER: Thank you for the opportunity to speak here today. I am Paul Melmeyer, vice president of public policy and advocacy at the

Muscular Dystrophy Association. MDA serves 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.

As stated previously, the Muscular Dystrophy Association does not participate in products for a specific advocacy [indiscernible], and thus will not make a specific recommendation on this drug. Instead, I will reiterate the flexible regulatory approach we expect the FDA and this advisory committee to utilize when considering this and all rare neuromuscular disease therapies.

FDA has continued to emphasize it has taken a flexible regulatory approach with previous ALS therapeutic reviews, and indeed, reconvening this committee to consider the new analysis plus descriptions of the agency's ability to withdraw judicially approved therapies from the market if the therapy does not show efficacy, both show the

agency's willingness in part from tradition.

We further 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 not only consider the use of one adequate and well-controlled clinical investigation plus confirmatory evidence to prove substantial evidence of effectiveness, but to do so flexibly, within serious, life-threatening, neuromuscular diseases.

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 when 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 again 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 the 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 assurances 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 traditional level of proof of effectiveness required in more common or less serious diseases. Analyses have shown that at least two-thirds of rare disease drugs are approved by the agency's flexibly considering whether the effectiveness 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 and must be addressed with the previous mentioned flexibilities. Today we again ask 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.

Just for those of you that are watching the agenda, we have six more presenters. S we're going to go for about another 20 minutes in the open session, so we'll be delaying the break.

Speaker number 19, your audio is now connected. Will you please introduce yourself, stating your name and any organization you represent?

DR. BEDLACK: Hello, everyone. My name is Richard Bedlack. I'm a professor of neurology and the director of the ALS clinic at Duke University in Durham, North Carolina. I'm also a consultant and a disease state speaker for various companies, including Amylyx, but I'm not being paid for my testimony today.

To start with, I want to thank the members of this advisory committee and also the FDA for their service. I understand that drug approvals are difficult. They require a balancing act between humanitarian need, science, and politics. I especially want to thank the four advisory committee members who felt, as I did, that the sum of this equation favored the approval of AMX0035 in March of this year. I trust that the new information the four of you have seen since then will only strengthen your original conviction, as it has my own.

For the six advisory committee members who voted no last time, I ask only one favor of you today. On behalf of the entire ALS community,

before you vote again, please read the editorial by Drs. Merit Cudkowicz and Jeremy Shefner, which was published in the Annals of Neurology in April of this year. In my opinion, these are the two most revered ALS trialists in the world, and they thoroughly debunked almost every scientific criticism this committee raised last time.

That really should be enough to change your minds, but in case it isn't, there is now an impressive new responder analysis showing more than twice as many patients on AMX0035 having slower than baseline progression during the study compared to those on placebo, and there are new survival analyses, suggesting benefits even larger and more clinically meaningful than what we saw last time. All that should be more than enough.

My final comments are directed to the FDA itself. Whatever this advisory committee decides, you, of course, will have the final say in whether patients with this horrific condition can try this promising new treatment. The fact that you're taking this unusual step of reconvening this

committee today tells me you're trying to be extremely cautious in your decision, and I suspect that has a lot to do with politics, the fallout of your approval of Aduhelm last summer.

I'm not an Alzheimer's expert, so I don't know whether that approval was right or wrong. But even if the latter, please remember, two wrongs don't make a right, and in your difficult job, there's always going to be a chance of making a mistake. It comes down to which mistake would you rather make, to approve AMX0035 now and find out in two years that it doesn't work? Now, I doubt many are going to be very angry because people with ALS got to try something that was safe and appeared promising in 2022.

On the other hand, can you imagine the mistake of saying no, and then getting confirmatory evidence in two years that this really did work, and realizing all those patients were much more disabled or even dead when they didn't need to be? I don't know how you'll be able to live with yourselves if you make that mistake. Thank you.

DR. MONTINE: Thank you.

Speaker 20, your audio is now connected. Will you please introduce yourself, stating your name and any organization you represent for the record?

DR. ABRAMS: Hi. Can you hear me ok? Good afternoon.

DR. MONTINE: Yes, I can hear you.

DR. ABRAMS: Hi. Can you hear me ok? Good afternoon? Hello? Can you hear me?

DR. MONTINE: Yes, I can hear you, Speaker 20.

DR. ABRAMS: I'm sorry. Can you hear me ok?

DR. MONTINE: Yes, I can hear you, Speaker 20.

DR. ABRAMS: Okay. Sorry about that.

Good afternoon, everyone. I'm Michael Abrams from Public Citizen Health Research Group. I have no conflicts of interest.

At present, we oppose FDA approval of AMX0035 as a treatment for ALS. We agree with the critique of FDA scientists detailed in their

briefing document, specifically in the first new analysis presented by the sponsor. They claimed to have used subjects as their own controls to compare response rates in the active drug group to the placebo group.

The FDA noted several limitations of: first, this post hoc analysis was not independent from the primary analysis of CENTAUR, and that cannot be considered confirmatory; second, the basis for comparing the treatment effect at 18 months instead of 24 months was unclear and inflated the effects observed; third, the analysis did not truly use subjects as their own controls; and finally, slope calculations were suspect. The FDA concluded, quote, "that these data appear limited in their ability to provide independent substantiation for the observed effect."

The second set of new analysis aimed to confirm the survival results using two different methods, one, historical comparison data, and the other, estimated survival using the Rank Preserving Failure Model. These analyses were deemed flawed

by FDA reviewers.

Specifically, the FDA noted the following regarding the natural history survival analysis. First, it was not randomized, not a randomized comparison; second, comparisons were made to controls from outside of the CENTAUR trial; third, the analyses were not prespecified; and finally there were concerns about multiplicity.

Regarding the rank preserving analyses, the FDA noted that it was based on, quote, "independent data and is simply using a new method of analysis for the same survival data presented in the original submission." Moreover, specific limitations of the rank preserving method included biases regarding recensoring that favored the treatment group and the unrealistic assumption that the treatment effect was proportional with time on the drug regardless of the start time for the drug.

Accordingly, the FDA stated, it, quote, "does not find these data sufficiently independent or persuasive." The final data analysis introduced by the sponsor examined biomarkers pertaining to

Alzheimer's disease. We agree with the FDA that the multiplicity of laboratory tests is questionable even regarding Alzheimer's, and even more speculative and indeed untested mostly as markers for ALS treatment effectiveness.

In conclusion, the new post hoc analyses of data from the already deficient CENTAUR trial failed to provide adequate confirmatory evidence of AMX0035's effectiveness as a treatment for ALS. Accordingly, we recommend that the committee vote no on the question before you today, and that the FDA not approve this medication for ALS at this time. Thank you very much.

DR. MONTINE: Thank you.

Speaker number 21, your audio is connected. Will you please introduce yourself, stating your name and any organization you represent for the record?

MR. WALLACH: My name is Brian Wallach. [Indiscernible].

MS. KLING: "My name is Brian Wallach. I am testifying for myself and for all ALS patients. I

am a 41-year-old father of 5- and 7-seven-year-old girls. I ask you to please stop multitasking, as I have three points to make.

"First, I am a human being. For this ADCOM, and the last, I have been robbed of the chance to address you face to face, which would enable you to see my humanity; to see my blue eyes and salt-and-pepper hair; to see my wheelchair and the way my face twists with every word; to see that this is not my voice, but that of a friend. This denial is wrong. It makes us an academic question rather than one that impacts real people and families, whose lives are in your hands.

"Second, I don't need you to protect me from myself. A surprising number of committee members who voted against recommending approval at the first ADCOM said they were doing so to protect patients. With all due respect, that antiquated paternalism is misplaced. I have studied this drug for four years, and lived with ALS for five. I know as much, if not more, about AMX0035 than many of you do. And I am not an anomaly. Just read the

1300 comments. ALS patients do our research. We don't want to try just anything, but we absolutely want to try a safe and effective drug like AMX0035.

"Finally, instead of thinking you are protecting me, I want you to recommend approval so that I have the chance to live. Canada approved AMX0035 with far less data than you have here. The main objections against approval are baseless, statistical arguments. After the last ADCOM, Drs. Cudkowicz and Shefner showed these arguments have no merit. They still don't. Everyone agrees AMX0035 is safe and well tolerated. The only question before you is whether there is sufficient evidence of effectiveness. You now have two data sets, CENTAUR and the open-label extension, that show a slowing of functional decline for ALS patients.

"As you know, ALS moves rapidly, is 100 percent fatal, and has no meaningful treatments. In this context, a drug that extends life, whether by 6, 10, or 18 months, has more than demonstrated sufficient evidence of effectiveness.

Moreover, this is no slippery slope, as this is the first-ever phase 2 to reach its prespecified primary endpoint of slowing the disease progression; the first ever, the first and only."

MR. WALLACH: There is only one right answer here.

MS. KLING: "There is only one right answer here. I just hope that you have the courage to recommend approval."

DR. MONTINE: Thank you.

Speaker 22, your audio is now connected. Will you please introduce yourself, stating your name and any organization you represent?

MR. DERBY: My name is Jeff Derby. I am 62 years of age. I live in White Rock, British Columbia, Canada. I am not receiving any payments from Amylyx for my presentation.

My journey began as most ALS patients, weakness in my hand and almost a year of visiting doctors, [indiscernible], three neurologists, before I was diagnosed with [indiscernible] ALS in July 2018. I have now lived with the disease of

ALS from August 2017, when I experienced my first symptom, which makes it five years ago.

Considering [indiscernible] the life expectancy of an ALS patient is 2 and a half years, what is so different for me? I know you are going to hear from many doctors today, scientists, and others that will provide you with the data, the numbers, graphs, and theory. I want to provide you with real-life information.

As I said, I was officially diagnosed in 2018, which at the time I was playing golf, ice hockey, going hiking, fishing, and [indiscernible audio distortion]. As years have passed on, I can no longer participate in those activities, but I can, with a [indiscernible], go for a walk, work on my computer, eat, talk, and during the day breathe without assistance. I was told by the doctor I wouldn't be here today [indiscernible]; in fact, by the averages, I should really be dead. What is so different for me?

You've heard [indiscernible] -- I have become friends with so many. [Indiscernible]

effective treatments today, the majority cannot walk, eat, talk, and have lost all their fine motor skills. Many require assistance in breathing every day, and most require 24-7 care. Some others I have gotten to know have sadly died over the past 5 years. What is so different for them?

Three months after my diagnosis, I was able to enroll in the Amylyx trial, AMX0035. After 7 months in the trial, I started to receive open label and have been taking ever since. As I was also taking the only other two approved treatments, riluzole and edaravone, as most others were, I believe the difference is AMX0035.

Why after 5 years and 4 months, would I be able to speak to you today, and so many can't even say the word "help" when they need to? Why can I eat when so many others have feeding tubes? Why can I breathe when many need full-time respiratory aid? And why is it possible I can stand and move when many ALS patients need to be lifted from bed? The only logical answer to me is my fortune to have been on AMX0035 for four years. Thank you for

listening to me today, and please give all ALS patients the same lifeline I have had. Thank you.

DR. MONTINE: Thank you.

Speaker number 23, your audio is now connected. Will you please begin by introducing yourself, stating your name and any organization you represent?

DR. ZUCKERMAN: I'm Dr. Diana Zuckerman, president of the National Center for Health Research. Our nonprofit center scrutinizes the safety and effectiveness of medical products, and we don't accept funding from companies that make those products, so I have no conflicts of interest.

My expertise is based on postdoctoral training in epidemiology and public health, as a former faculty member and researcher at Yale and Harvard, and my policy work on FDA issues. I'm currently on the board of the nonprofit, Alliance for a Stronger FDA, which educates Congress about a need to financially support the work of the FDA.

ALS is a terrible disease, and what's needed is a more effective treatment with clinically

meaningful benefits. We need better evidence for AMX0035 because if it's approved, it will undermine randomized-controlled trials of ALS treatments. Even if the U.S. enrollment in the PHOENIX study is completed, that doesn't mean the follow-up has been completed. And what about placebo-controlled studies of other ALS treatments? Nobody wants to be in a placebo group.

Canada's conditional approval standards are lower than those for FDA full approval, so we shouldn't be influenced by Canada's decision. Sponsors always have the option of voluntarily removing the product from the market, but that rarely happens, and only under very strong pressure from FDA or from lawsuits. In this case, FDA has repeatedly told Amylyx what kind of study design and analyses would be persuasive. Amylyx repeatedly rejected those suggestions, and currently disagrees with FDA's criticism.

Today we all heard Amylyx tell us that they believe their data provide, quote, "a robust confirmation," unquote, that their drug worked, so

it seems naive to think that Amylyx would voluntarily withdraw their drug from the market unless the PHOENIX study results were really terrible, and none of us want that. What we want is better evidence, and until that's available, patients deserve free access through clinical trials and through FDA's expanded access program for experimental drugs.

In conclusion, I know your votes will be tough today. We all wish the company had done a better job of gathering solid evidence, and that's on Amylyx to fix, not on the FDA to excuse. Meanwhile, isn't there a data monitoring committee for the PHOENIX study to consider earlier outcome, perhaps in just a few months, so we'll know more about the effectiveness of this drug? Thank you very much.

DR. MONTINE: Thank you, and we'll go back to speaker 1.

Forgive me, speaker 1, for the awkwardness at the beginning. Your audio is now connected. Will you please introduce yourself, stating your

name and any organization you may represent for the record?

DR. SIMMONS: Thank you. I'm Dr. Zachary Simmons. I'm a professor and vice chair for research in the Department of Neurology at Penn State University where I direct the ALS Center. I've been involved in ALS care and in multiple clinical trials over the past 30 years. I have received consulting fees from Amylyx and other companies involved in ALS treatment, but no payment for this testimony today, and I was not involved in the CENTAUR trial.

As a clinical researcher, I find the evidence for the efficacy of AMX0035 compelling. The primary outcome measures used the revised ALS Functional Rating Scale. It's the most widely accepted instrument for outcomes in ALS clinical trials. The statistically significant slowing of disease progression compared to placebo is published in the New England Journal as impressive and supported by sensitivity analyses, correcting for concomitant use of riluzole with or without

edaravone.

Secondary outcome measures of strength, vital capacity, hospitalization, and survival all trended in the same direction, and then two additional studies published in Muscle and Nerve showed a survival benefit of at least 6.5 months, and possibly as long as 18.8 months compared to placebo.

Having gone through the disappointment of dozens of negative studies, or studies where one outcome measure looked promising but others showed no benefits, these results impress me. But you know the data. I'd like to urge you to look at this from a different perspective.

Much of my research in ALS has been on quality of life. Quality of life in individuals with ALS is not necessarily dependent on physical function, but rather on psychological, social, spiritual, and existential factors. For such factors to have the greatest impact, individuals with ALS need more time to adapt to their losses and to be able to reframe those aspects of their

life that have the greatest meaning.

Slowing of disease progression and extension of survival are, thus, particularly important. Giving persons with ALS additional time to benefit from the support of those around them, to enjoy the beauty of their surroundings, and to live to celebrate meaningful life events with those they love, would contribute greatly to the quality of life.

Importantly, healthy individuals usually rate the quality of life of persons with ALS lower than those individuals themselves rated. Healthy individuals may not perceive those with ALS to have a good quality of life, but that is highly judgmental and often erroneous. In summary, I find the evidence on efficacy of AMX0035 compelling and the potential impact on quality of life substantial. Thank you very much for your time.

DR. MONTINE: Thank you.

The open public hearing portion of this meeting has now concluded and we will no longer take comments from the audience. 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're going to take a 12-minute break, so will the panel members please return at 5 minutes after the hour? Please remember that there should be no chatting or discussion of the meeting topics with other panel members during the break. Please reconvene at 5 minutes after the hour. Thank you.

(Whereupon, at 4:54 p.m., a recess was taken.)

Clarifying Questions (continued)

DR. MONTINE: Hello, and welcome back. As promised, we're going to take the next approximately 15 minutes and return to the panel's questions for Amylyx, or if there are additional questions for FDA. But I believe everyone got their questions in, in that session, but I know the question period for Amylyx was not sufficient for the number of questions that the committee had.

So we'll start there, give ourselves 15 minutes there, and then proceed. If you're not

noticed, please mute. We're picking up some background.

So yes; Dr. Follmann, you've been very patient, I know, so thank you so much. Would you please start us off?

DR. FOLLMANN: Yes, thank you. I'm happy waiting, and even happier to pose my question. This is to Amylyx.

The FDA in their briefing document criticized the crossover-adjusted analysis because the placebo crossovers were healthier than the placebo dropouts, and I wondered how you had addressed that, or if you had thought about that in your crossover-adjusted analysis. Over.

DR. TIMMONS: Sure. In terms of the RPSFTM analysis, that is looking at all participants. It maintains the randomization, so we're looking at everyone, not just subgroups. So given that the randomization is maintained, those subgroup differences would not necessarily apply in terms of being a criticism of this analysis.

DR. FOLLMANN: But isn't it true that the

people who cross over and get treatment, you end up under this model, essentially reducing their time to death on placebo, the time of death to placebo [indiscernible], and there's not a similar kind of adjustment done for the placebo people who don't cross over. So I think it would have been helpful to adjust using baseline covariates or something like that.

DR. TIMMONS: Sure. The RPSFTM analysis in terms of covariates that are used in that and also in the ITT analysis, we've done the analysis both with this baseline ALSFRS-R with and without that as a covariate. We don't really see a difference between the ITT results, and then, of course, similarly with the RPSFTM results as well.

DR. FOLLMANN: Okay.

I have Dr. Schoenfeld as well, if there are any other more methodological questions about the RPSFTM, that he could answer statistician to statistician.

DR. FOLLMANN: No. I think that's sufficient for me. I think, basically, you did as

best you could, which is to adjust using baseline covariates to take into account the fact that not everyone in the placebo arm crossed over, and that the sicker patients probably were the ones who were less likely to cross over.

DR. MONTINE: Great. Thank you both.

DR. TIMMONS: That's correct. And that's also the reason we did the other two analyses with the external controls just to provide that further support; different analyses, different methodologies.

DR. FOLLMANN: Thank you.

DR. MONTINE: Excuse me. I didn't mean to interrupt you. My apologies.

Dr. Fischbeck, please.

DR. FISCHBECK: Yes. I still have a couple of questions or comments, and one minor point. Maybe I could just hit one or two of them now, and then come around again if there's time; that's if I find it again.

We were asked about whether this is an adequate and well-controlled study, and there's one

thing that hasn't exactly come up here today, is the randomization error; so the fact that the first 27 kits were sent out without randomization, and there was an analysis done to remove them. This still showed significance, although not quite as good a p-value as before.

At the same time, there was also a problem with patients starting edaravone during the course of the study. I think that also has an effect, or could have an effect. There were 13 patients calculated that were in that category, and when they were removed, the same thing still; the p-value went up 0.04 with the edaravone.

I guess the question I have is what if you remove both those who had a problem with the randomization due to there's a shipping error, I guess, or the randomization error, and those who had a problem with starting edaravone during the study, which could have had an effect on the outcome, or given that it's FDA approved treatment.

DR. TIMMONS: We haven't done that specific analysis in terms of removing both together at the

same time. A couple of points that may be helpful here, one is when we look at that early randomization error and we look at the baseline characteristic for the entire group and the group who were impacted by that error, we see basically the same baseline characteristics. So the error itself did not impact the match between the two groups, including in terms of baseline use of riluzole and edaravone. But to your key question, we did not do the specific analysis both together; only the individual ones where we still see consistent results on the ALSFRS.

DR. MONTINE: Thank you.

DR. FISCHBECK: A minor point I was going to say is a couple of times it was mentioned that ALS is universally fatal, but traditionally we think of about 10 percent having long-term survival, and I've seen patients who survive out decades, without dying. It occasionally happens, although I yield to others who are more actively involved in ALS patient care now, and whether I'm wrong there; whether these patients might have been

misdiagnosed.

DR. MONTINE: Thank you. Thank you both.

DR. TIMMONS: You're just commenting? Got it.

DR. FISCHBECK: Does Dr. Cudkowicz or Dr. Paganoni have something to say about that, if they're still here?

DR. TIMMONS: Yes, absolutely.

Dr. Cudkowicz?

DR. CUDKOWICZ: Thank you. Yes, it's still a uniformly fatal illness. Even the people who have lung longevity die from the ALS. However, in this study, the inclusion criteria were designed to pick fast-progressing people, and those few people that can live longer would have been excluded from the study.

I also want to just add on the last point that the randomization error -- and I brought this out of my editorial -- was exceptionally well handled. This was something that was kept -- until after database blocks and after results, and was handled exceptionally well, and [indiscernible] --

removed, and that there's no difference in the end result.

DR. FISCHBECK: Okay. Thanks.

DR. MONTINE: Thank you.

Dr. Caleb Alexander?

DR. C. ALEXANDER: Yes. Can you hear me?

DR. MONTINE: I can.

DR. C. ALEXANDER: Can you hear me?

DR. MONTINE: I can hear you.

DR. C. ALEXANDER: Great. Sorry. There's a little bit of a delay.

I had a quick question, and then a little bit more detailed one. The quick one just has to do with edaravone, and I was just trying to reconcile the report in the New England Journal of Medicine; that, no, that analyses corrected for edaravone did not reach statistical significance with briefing documents provided today, that seemed to suggest that the use of concomitant medicines didn't impact the interpretation of the findings. So I just wondered if you could clarify that.

DR. TIMMONS: Sure. The New England Journal

of Medicine article is looking at the first 24 weeks and the ALSFRS-R data. The sensitivity analyses that we presented there are some of the same ones that we presented today, and then we also did additional assessments as well; and pulling these up here for the ALSFRS-R.

The adjusted for time on edaravone and riluzole are the sensitivity analyses that are reported in that publication. We also talked about removing participants within study edaravone starts [ph], and that's a new analysis that we're presenting today, and then also adjusting for baseline use. So that's categorical; are you on it or are you not? And again, we're seeing a consistent effect size here across these sensitivity analyses.

DR. C. ALEXANDER: Okay. Thank you. That's helpful.

Then the other question had to do with slide 55 of the briefing document, slide 55 of 66, entitled, Historical -- that's it. This is one of the things that I think is most -- it's an

interesting and sort of perplexing point to me, which is that there are these whopping survival differences in the open-label study, and yet one doesn't see these in the randomized portion, nor does one see statistically significant findings of the secondary endpoints in the randomized, 24-week phase, although I think some of these may have been nominally significant.

So my question is, I'm both interested in what you think mechanistically explains the fact that these two curves are essentially on top of each other until month 7, 8, or 9, when they start just this whopping divergence.

Then the second part of the question is, one of the assumptions, if I understood it correctly, to the RPSFTM model was that survival time benefit was proportional to time on the drug. So I just wondered how you think about that type of assumption in the context of this type of plot.

DR. TIMMONS: Sure. In terms of what we're seeing here for the plot, a reminder that a specific inclusion criteria for the CENTAUR study

is that participants were to be expected to live through the first 6 months, so that's why we do not see a survival difference in the first 6 months of the study. As a, reminder, the ITT overall survival analysis, all participants are still randomized. They have not been unblinded. Neither have the investigators been unblinded. We're comparing the as-randomized groups in that long-term overall survival analysis as well, too.

I'd like to have Dr. Berry comment from a clinical perspective in terms of the curves separating later, et cetera, his interpretation there.

DR. BERRY: Hi. I'm James Berry, an ALS researcher and clinician at Mass General Hospital. I appreciate the question. I think it's a good one. It's one that I think many of us looking at the data have thought about, how do we see these fairly large survival differences when the difference in most people receiving drug, either at the beginning of the randomized trial or at the beginning of the open label, which is only a

6-month difference -- I think in walking through this data, number one, it's robust across the number of analyses, and I begin to think of analogies.

I think the simplest analogy that I came to is that while it seems remarkable that we could see almost a 5-month difference in survival with just a 6-month difference on drug, much of that may have to do with when the drug is taken. And the analogy would be that if I have a headache today and I take Tylenol today, it will help my headache. If I take that same Tylenol tomorrow, it very well may have no effect on my headache.

That's a simple analogy, but at the same time I think it captures the fact that we may need to treat this disease early, and that when we treat it later, we may not see that same effect.

DR. MONTINE: Thank you.

DR. TIMMONS: Great. And as a reminder --

DR. C. ALEXANDER: Yes. I guess I'm sort of perplexed mechanistically -- I'm sorry for the delay. I guess I'm just perplexed a little

mechanistically of what's going on, where if you look at the plots, they're sort of linear separation of maybe the primary outcome, and yet when you look at survival, again, the plots are sort of lying on top of each other.

Then I guess the second part of the question has to do with how this affects the assumption, if I understood it correctly, of the RPSFTM, which relied on, I think, some untestable assumptions but including that survival time benefit was proportional to the time on the drug.

DR. TIMMONS: Yes. In terms of the RPSFTM question, I will ask my statistical colleagues to help with the assumptions there and how we interpret those.

Dr. Schoenfeld?

DR. SCHOENFELD: Hi. I'm David Schoenfeld. I'm an emeritus professor at the Harvard Medical School, and I've been involved in ALS trials over the last, I don't know, 30 years, or something like that. But in any case, the RPSFTM model, the way to think of it is that if you're being treated,

basically time slows down for you. So in other words, as you go along, your time is going along, and then as you suddenly begin treatment, the accelerated failure time model, which is what this is based on, time is slowing down, so then you would live longer while you're being treated.

That kind of model would allow, for instance, the curves to be on top of each other for the first 6 months. The time is going faster for the placebo patients, and then 6, 10 months, 11 months later, the fact that time has gone faster for them means that they begin to die much sooner. That's the assumption of the model.

The model is also fairly robust to covariate differences because each person is looked at separately in the sense that time moves for each person differently. So if people have shorter survival, then they're getting a benefit based on that expansion factor. I hope that's explaining this. This is a complicated model, and it's a little hard to understand. Thank you.

DR. MONTINE: Thank you.

DR. TIMMONS: To understand the different models, we did the two additional control analyses just to test these different assumptions within each of the models.

DR. MONTINE: Thank you.

Dr. Nath?

DR. NATH: Yes. Avi Nath here. I was wondering are there any plans for interim analysis in the PHOENIX study.

DR. TIMMONS: There is not a plan for an interim analysis in the PHOENIX study. That is a 48-week study, and by the time that there was enough power to perform an interim analysis that would provide useful information, the study would be quite near completion. This was discussed with the FDA I believe last year, and it was determined that an interim analysis would not be done, especially to keep data integrity of the study.

DR. NATH: Thanks.

DR. MONTINE: Thank you.

If I may ask, for some clarity on the biomarker data, there's a large set of molecules

that were reported. They were designed for an Alzheimer's study, but how many, other than YKL-40, overlaps is an accepted biomarker in patients with ALS?

DR. TIMMONS: I'm showing the list of biomarkers here, and I think one of the people that would be best to answer this question is Dr. Bowser, who is an expert in biomarkers, both ALS and Alzheimer's disease. So I'll turn it over to Dr. Bowser to introduce himself and answer your question.

DR. BOWSER: Hello. Thank you very much. Robert Bowser. I am chief scientific officer, professor, and chair of the Department of Translational Neuroscience at the Barrow. Neurological Institute. I'm also founder of nVector, which is a biotech company that has received and analyzed the samples from the CENTAUR study, the plasma samples for both neurofilament and YKL-40.

To answer the question, of this list, YKL-40 is the most widely reported and published biomarker

in the world of ALS when looking at just this list. Second, total tau levels have been looked at in a number of studies and actually followed in a prior clinical trial about 12 years ago. Phosphorylated tau doesn't change much, so people look at a ratio of total tau to phosphorylated tau, which does change given the total tau changes in ALS patients.

The A-beta ratio has been published once or twice in ALS, and it does show a difference over time in ALS patients. Neurogranin, which is more of a synaptic integrity biomarker, has not been explored much in ALS, and the same with FABP3. So both of those have not been reported much in the literature of ALS.

DR. MONTINE: And of the list of ones that has not significantly improved, are any of those commonly --

(Crosstalk.)

DR. BOWSER: Yes. Obviously, neurofilament is probably the best studied out of the whole list of biomarkers here in the world of ALS. IL-6 has been shown to be changed in a subset of ALS

patients. MCP-1 has been shown to be altered in ALS patients; let's see, GFAP also, but more traditionally that is looked at in tissue samples as opposed to biofluids. IL-8 has been shown in one or two studies, but not a substantial amount of studies.

So again, NfL is the most robust of that list, but to me, actually, this is somewhat supportive. You have a study, same drug, different neurologic condition, no change in neurofilament in both the CENTAUR ALS study as neurofilament measured in blood and the Alzheimer's disease study here, where it's measured in CSF.

DR. MONTINE: And has that pattern been seen before, of no change in neurofilament but change in YKL-40?

DR. BOWSER: Actually, it has. Probably it's actually a fairly recent publication where -- it's actually from the Belgian group. They looked at adult SMA patients treated with nusinersen for almost two years. In that study, what they saw was a modest but not significantly

changed levels in neurofilament, but a change in YKL-40 in response to drug. And YKL-40 was the only biomarker that actually correlated with measures of clinical improvement in that patient population.

DR. MONTINE: Thank you so much.

DR. BOWSER: Sure thing.

Questions to the Committee and Discussion

DR. MONTINE: Okay. So we'll now progress in our meeting.

The committee will now turn its attention to address the task at hand, a careful consideration of the data before the committee, as well as the public comments. We will now proceed with questions to the committee and panel discussions. 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 each question, we will pause for any questions or comments concerning its wording, and then open the question to discussion.

Question 1 discussion, discuss the strength of the currently available data regarding the effectiveness of sodium phenylbutyrate/ taurursodiol, AMX0035, to include the new information submitted and the information presented at the March 30, 2022 PCNS meeting. The discussion may include considerations regarding the unmet need in amyotrophic lateral sclerosis, ALS, the status of the ongoing phase 3 trial, and the seriousness of ALS.

Any questions or comments concerning the wording?

(No response.)

DR. MONTINE: Hearing none, then we open this for discussion.

Dr. Fischbeck, you have your hand raised?

DR. FISCHBECK: Yes. I'm probably talking too much here. I for one was really struck by the comments submitted by the patients and families, the 1,288 comments. I can't say I got through all of them, but enough of them to get a sense of where the patient population's coming from; and then

really striking today with the public session, to have a few patients, and then a number of leading clinicians in the field were speaking in favor of this. It looks to me like a flawed study, but it certainly has a lot of patient interest and clinician interest in approval.

One thing I was struck by -- and this is the last question I was going to ask of the company, and do they have any thoughts, but it's really my own -- is we spoke last time about GI events and whether that could reflect to unblinding. The company reported a survey that was done of patients and physicians involved about whether they were able to guess correctly whether they were on placebo or active agent, and they couldn't. It wasn't any different from chance, which turning that around -- aside from the unblinding question with the GI effects, which I don't think was a big factor here -- the patients didn't know whether they were on the drug or not, and I think that runs counter to a lot of what we're hearing.

The patients and the clinicians couldn't

tell the difference while they were taking the drug, and that turns around a lot of what we heard in the testimonials about asking for this drug to be approved because it was making them better. Maybe it was just too subtle an effect on increasing survival, but even then, I think they should have known if it was really having an impact on the disease. They should have known whether they were taking it or the placebo. That's all I have. Thank you.

DR. MONTINE: Alright. Thank you for your comments.

Dr. Caleb Alexander, you're next.

DR. C. ALEXANDER: Yes. Well, I agree with a lot of what was just said, including how compelling the perspectives are that we've heard from many that have been personally impacted by ALS. It seems to me that an awful lot hinges upon the adequacy of the open-label ITT data, given that's what's being proposed as the confirmatory evidence. And I'm a little unclear, from the FDA's perspective, how commonly confirmatory evidence is

derived from the same study that's being used as the pivotal study in this instance.

I'll say I think the FDA's initial description of this study was a little generous in calling it a successful study while glossing over a large number of concerns that were thoroughly explored by this group during the last committee meeting and also briefly touched upon by the FDA biostatistician during this meeting. But I think, ultimately, if we accept the single study as having many substantive concerns but also being promising, and this question arises, is there sufficient confirmatory evidence, then I think a lot is resting on the adequacy of the open-label ITT analyses.

The new information shared today are new analyses of old data, essentially, as the FDA has pointed out, and they were not prespecified, and I think that's the real concern about them. There's a reason that in games, and sports, and otherwise, the rules are decided before the game, not after the game; not after the plays are made. So I think

the concern is just that while new information has been shared, it's information that's based on essentially post hoc analyses that depend upon a lot of decisions and assumptions that could affect the results of those analyses. Thank you.

DR. MONTINE: Thank you.

We have two more, and then hopefully we can get to a more open discussion. I know it's a little stilted doing this remotely.

Dr. Apostolova, you're next.

(No response.)

DR. MONTINE: Liana, you may be muted.

DR. APOSTOLOVA: I'm double-muted. Sorry about that.

Overall, the evidence we saw in the March 30 meeting and today presents modest effectiveness at best; and really, a drug that is targeting a neurodegenerative disorder in a disease-modifying way, we shouldn't expect improvement, but slower decline. The lack of patients, physicians, guessing right whether they're on the drug really helps with the truly blinded assessment of outcome,

so that does not bother me.

I also feel that Amylyx showed some confirmatory evidence today to external control samples, one notably with 10,000 subjects, while applying propensity score matching to adjust for disease risk, durability, and disease progression rates. And while these data do not quite meet the criterion of being forcefully persuasive, the data are nonetheless reassuring.

The biomarker data on the other hand appeared weaker, as it suffered from the shortcoming of being collected in a different neurodegenerative condition, and it is not really clear if any biomarker movement in Alzheimer's is relatable to ALS. Yet, I am somewhat reassured that if an approval is issued, it can be withdrawn in the future, and further reassured that the side effects from this therapy are not harmful in any significant way, and I'll stop there.

(Pause.)

DR. APOSTOLOVA: Hello? Can you guys hear me?

MALE INVOICE: I wonder if our chair is muted.

DR. SEO: Good afternoon, everyone. Dr. Montine is trying to reconnect. We'll just give him a moment. Thank you.

(Pause.)

DR. C. ALEXANDER: Well, should we just have another committee member speak, given that the time is valuable?

DR. R. ALEXANDER: Yes. This is Dr. Robert Alexander. I'll comment. No one else wants to jump in.

I just want to say in terms of what we heard today and what was truly new, we didn't hear much about the responder analysis, but I think the fact that it wasn't discussed is probably an indicator that it doesn't really contribute much to judging whether this drug deserves approval or not.

The biomarker data I think is not new because I think it was mentioned at the previous meeting that the biomarker change that was observed in an Alzheimer's study, it does help provide some

indirect evidence that there is a CNS effect, but it doesn't necessarily tell you that you had appropriate exposure for ALS. I'm not sure what to make of the new report about the YKL-40 since it doesn't really represent a change from baseline, at least as I understand it, just comparing the values at week 24.

But I think there is probably more evidence now to believe that there is a real benefit on survival for patients that received Amylyx first versus the ones that received placebo first. I think the activity analyses that were performed, in particular removing participants who had in-study edaravone starts and the comparison to the natural history, even though it wasn't prespecified is supportive that there is a real difference.

I think there's still substantial uncertainty around the drug's efficacy profile, but I do believe that the information that we received is supportive that there is an unexplained survival benefit which can't be -- I mean, it doesn't seem to be evidence that's due to disease heterogeneity

between the treatment groups, so in that sense, it helps you attribute it to the drug. Thanks.

(Pause.)

DR. C. ALEXANDER: Thank you.

It looks like we're still waiting for Dr. Montine, and this is Dr. Alexander.

Dr. Follmann, perhaps you want to speak?

DR. FOLLMANN: Yes. Thank you. I just wanted to raise a few points. I absolutely voted for approval in March, and I won't reiterate the primary analysis. I think the FDA has sort of accepted that as showing having met its mark.

The benefit on survival that was presented in March I thought was strong supportive evidence. It was based on a conservative ITT analysis, and for me if you're going to have a trial to an open label study, what is a stronger endpoint and more objective endpoint than survival, which was ascertained in every patient but one.

The FDA does have a concern about multiplicity, and this wasn't prespecified, but personally, this would be the endpoint that I would

look for in a study like this for supportive evidence. So that, to me, in totality, along with the rare disease, the unmet need, et cetera, caused me to vote yes in March, and I think it aligns with the flexibility that the FDA talked about today.

Just a few comments about the analysis that we've seen today, I think the major addition is really just a different estimate of the placebo-controlled benefit of Amylyx on survival. Before, under the conservative ITT approach, it was about 5 months; now it's closer to 10 months. I like the sponsor's crossover-adjusted analysis. This is the way I would approach it if someone said, "Dean, there is a lot of crossover in the placebo arm. What's a good estimate of the overall survival advantage?" I would say, and I do believe -- [inaudible – audio break] -- that it is to 4 months. Having said that, though, I do take the FDA's point that the certainty about that really hasn't changed, and I think that's properly reflected in the p-value being still just under 0.05.

The two external control studies, I don't really like external control studies usually, and I discount the p-values that were presented from those studies, but I feel that they do support the crossover-adjusted analysis estimate of about 10, so I'm more comfortable with that. The biomarker analysis and the responder analysis didn't add much for me.

I would just make a final comment about the PHOENIX trial. I thought about that some in March, and ultimately I decided that we shouldn't really think about it. I mean, what does it help us with the decision and the evidence we have today? I think it might make it easier to try and abstain or something, which I [inaudible – audio breaks].

I also, I guess, echo a comment that I had heard earlier today. The drug is not harmful. It seems like it has a benefit. There's not a safety signal here, so in the worst-case scenario, if the PHOENIX trial does show lack of benefit, it's not like we've harmed patients by licensing it now. So I'll stop there.

DR. MONTINE: Thanks.

This is Tom Montine again. I apologize. The call got dropped, and it took me a moment or two to get back. But by some miracle, my iMac stepped in, so I heard everything people said even though the phone disconnected, so thank you for those who stepped in. My apologies.

While I have the floor, I could ask for some guidance from the group. The biomarker data is not helping us with medical meaningfulness like the trials are, but it impressed me that whatever pathways underlie elevating YKL-40, they could be shared by these two diseases. So does the biomarker data have any biological relevance for us? Does it tell us that perhaps this medication is hitting a pathway that has shared relevance in these two diseases, or you think that's taking the data too far?

DR. NATH: This is Avi. I'm still quite concerned about the biomarker data. The problem is that it's only at a single time point, and I would have liked to see that there were multiple

time points. A lot of these biomarkers fluctuate. We don't know. You could measure these things 3 hours later, and you probably come up with a different result. So if they would have measured them at multiple time points and shown us change over a period of time, that would have been more convincing.

It's also concerning that the neurofilament levels did not change. In fact, if you look at that Alzheimer's study, look at that table there that they presented, even though they say it's not statistically significant, actually the neurofilament and GFAP levels went up in patients with Alzheimer's by several-fold -- the mean values didn't [indiscernible] -- and that indicates axonal damage as these neurofilament levels do, and GFAP suggests that there is glial cell reaction taking place. So I won't rest all my decision making on the biomarkers for sure.

The other thing that concerned me was that they added these natural history studies but never really explained why the placebo group is so

different than all these natural history studies. Maybe Dean would comment on it. If you do a statistical analysis, you might actually see a placebo response compared to the other natural history studies, so that makes me discount the natural history study. And then if you do that, then you're just left with the placebo and the drug data, but the data they represented last time. Over.

DR. MONTINE: Thank you. That's very well reasoned.

Dr. Traynor, I believe you have been waiting to comment.

DR. TRAYNOR: Hello. Hi. Bryan Traynor here. I'm just wondering, we've been talking about lack of side effects for the patients they put on this particular medication, but I'm wondering, there is another aspect to this, and that is the financial aspect.

Are we allowed to ask the company directly about this? Because my concern will be are they going to price it so that they recoup their money

within the three years until they know whether the phase 3 worked or not, or are they going to price it on the assumption that it is going to work in the phase 3, and they're going to continue on for 10, or 20 years, or whatever the patent is? Thank you. I don't know if that's an appropriate question in this context.

DR. C. ALEXANDER: It's not a regulatory consideration. I'm sorry to interrupt. This is Caleb Alexander, but it's not a regulatory consideration. You know --

DR. TRAYNOR: But it does --

(Crosstalk.)

DR. C. ALEXANDER: -- the FDA doesn't consider dollar signs, and I don't see --

DR. TRAYNOR: Yes, Caleb. Thank you. But it does actually come in to this.

DR. C. ALEXANDER: It's not a scientific matter relevant to the question at hand.

DR. TRAYNOR: Yes. Okay. I mean, that's your opinion. I wondered whether --

DR. C. ALEXANDER: Say the company offers to

give it away for free; does that affect -- I'm sorry. Go ahead.

DR. TRAYNOR: We're not talking about them giving it away for free. You're talking one extreme. I'm talking -- you can't argue an extreme. I mean, that's not appropriate.

I mean, what we're talking about here, ultimately, is we're trying to address the question whether the benefits outweigh the real side effects that are potential here and the risk that this is a false positive. So the question becomes, what other aspects do we have to consider in that? And there are opportunity costs that come along with this as well. So if we give this drug, are we missing an opportunity to run other clinical trials of other agents that might work or that might be better? I'm not so struck with that opinion that this is not an important point.

DR. C. ALEXANDER: I mean, listen. There are lots of potential spillover effects of approval, and there are lots of potential collateral effects of approval, and there are lots

of potential collateral effects of non-approval. But the question for the committee is whether or not there's substantial evidence of effectiveness, or if you like, safety and effectiveness, but no one is really arguing that this product is unsafe.

So the real question is, is there substantial evidence of effectiveness? That's the question before you, and the FDA has done a very nice job of laying out what those criteria are and how typically substantial evidence is appraised, and so it's up to us to decide how we feel about that. But financial toxicity --

(Crosstalk.)

DR. TRAYNOR: But, Caleb, that's your opinion.

DR. C. ALEXANDER: -- is a bit astray from whether or not --

DR. TRAYNOR: I'd like to hear from the chairman or from the FDA.

DR. C. ALEXANDER: -- there's substantial evidence.

DR. MONTINE: May I, please? This is a

great discussion. Is there a colleague on the line from the FDA who could guide us?

DR. DUNN: Yes. Dr. Montine, thank you. This is Dr. Dunn. I'm happy to address that. I want to be respectful of the committee's ability to have a discussion that ranges where they feel that it needs to, to address the question.

Dr. Traynor, I'm listening closely to you. I will briefly simply clarify -- not really clarify, but simply supplement the comment that Dr. C. Alexander made regarding the fact that cost is not a consideration in our scientific deliberations and decision making. That is absolutely true.

So if there's any confusion on any part -- I'm not suggesting there is confusion. If there is any confusion on the part of a committee member about whether that is a relevant consideration for us in our decision making, it is not.

Dr. Traynor, I don't mean to imply that you have any confusion about that. Again, I understand

what you're getting at. You may certainly, again, ask for clarification on issues from the company that you think are relevant to the question. And again, I wouldn't presume to talk to any members what they can and can't discuss with each other, but I do want to make clear the point that cost is not a consideration in our assessment of the scientific evidence.

DR. MONTINE: Thank you, Dr. Dunn.

DR. DUNN: Very good, Dr. Montine. Thank you.

DR. MONTINE: Thank you.

MR. WESTON: Tom, this is Mark. I've had my hand up for a bit, and being the non-doctor on the panel, I'd like to weigh in a little bit there.

We're focused on the first question, which has to do with the robustness of the study and the data and so forth. I think we can talk about this for a few days, and still all of us agree that the data could be better. The study could be better. We could sort out some of the finer statistical and analytical techniques, and find different ways to

do them, and the result's going to be the same. The drug is safe and it might help people. So maybe we should put equal focus, as we deliberate, on the other considerations, unmet need in particular.

We have two drugs. Some would say three, but one drug administered one way; two drugs with a choice for administration. That's not a lot of choice; right? So maybe we talk more about unmet need, which is not exactly something we can quantify nearly as well as p-values and that sort of thing.

So I'm going to save some of what I want to say until we get into discussion, but it seems to me we're actually bridging from questions to the committee, in the committee discussion, before we get to the vote. Thank you.

DR. MONTINE: Thank you. Yes, I think that's great advice, Mr. Weston, trying to stay focused on the totality of the question in front of us.

The summary that Dr. Nath gave, at least of

his opinion, resonated with me that as we go through the new information and the new data presented today, I'm not sure that we're actually that much farther along than the information that we had in March. I'd love to hear people's opinion about that, and then as Mr. Weston just said, in addition to that, the importance of the unmet need in ALS, and then the third part is the context of the ongoing phase 3 trial.

So I'll stop summarizing, and I'll just move to the next.

Dr. Dayno, please?

DR. DAYNO: Yes. Thanks, Dr. Montine. This is Jeff Dayno. Maybe moving us towards the regulatory issues and transitioning to the broader discussion, I just wanted -- and maybe it's timely -- to take a moment to share a few thoughts, kind of representing an industry perspective in the context of these very challenging issues that we are discussing with regards to the data and overall risk-benefit.

First, also I want to thank the Amylyx team

and members of the FDA for their excellent presentations, and I also want to thank and acknowledge Dr. Dunn for his introductory remarks. I think he framed the issues very effectively of what we're kind of grappling with today, and several which were expanded upon by Dr. Buracchio in her comments. And I just want to highlight, I think, a few key points based on the FDA's comments.

First, I think it's important to understand the importance and the distinction between statistical significance, which you've been speaking a lot to, and clinical relevance. Then beyond that, Dr. Dunn alluded to another level of distinction between statistical significance and statistical considerations, another really interesting point he made, and those which are based on both scientific and clinical judgment; and obviously clinical perspective and clinical judgment in the context of a rare and fatal disorder becomes very important.

I think most importantly, I think we all

appreciate the comments from both Dr. Dunn and Dr. Buracchio related to regulatory flexibility, and I know that we'll be speaking more about this in the context of the impending vote; but the importance of regulatory flexibility in the setting of a serious and life-threatening disease like ALS, which is one that has both not only a significant but an urgent unmet medical need, and I think actually the FDA alluded to that. Then in this setting, the FDA has acknowledged they have the opportunity to exercise both the maximal and broadest degree of regulatory flexibility, and I think that's important to keep in mind.

With regard to regulatory flexibility, FDA in the briefing document and their comments spoke to precedence in this disease area in ALS, and I think riluzole is a good example of that, and an important one. The application included two adequate and well-controlled trials, both of which failed to meet the prespecified primary endpoint that assessed survival. The FDA thought that a different alternative test was appropriate, and

conducted a post hoc analysis using the alternative statistical testing, which resulted in exploratory findings of nominal significance, and that's the data that led to the approval of riluzole.

Then lastly, I think Dr. Dunn mentioned a really interesting concept during his comments around regulatory flexibility related to the need for increased regulatory tolerance in the setting of uncertainty; I think a setting that obviously we're in and discussing today. In that setting that we're discussing, it means increased tolerance for both a false positive outcome if AMX0035 is approved during this review cycle, then the phase 3 PHOENIX trial proves to be negative, as well as increased tolerance for a false negative if it is not approved during this review and the PHOENIX trial reads out positive.

I think really important and critical in that setting, it's really critical to listen carefully to the patients and the patient community, as well as the clinicians who are taking care of patients with ALS. And we heard from both

of those groups, and they're both key stakeholders in this discussion, and we heard from them during the public hearing today.

Just to close my remarks, I think all of this is consistent with FDA's initiative as part of the 21st Century Cures Act, which identifies the importance of using real-world evidence in assessing the approvability of investigational agents, as well as the value of the patient's voice in the context of patient-focused drug development, especially in the setting of rare and fatal diseases with significant unmet medical need. Thank you.

DR. MONTINE: Thank you.

We need to watch our time, so I guess I'll take my chair's prerogative and try to refocus us again on the discussion point. The point is effectiveness. Has the new information that we received today, the post hoc analysis, the biomarker data, all that -- again, remembering what we had in March, is anyone -- who is strongly persuaded by the new information of effectiveness?

DR. R. ALEXANDER: Dr. Montine, this is Robert Alexander. I just want to respond to Dr. Nath's comment since he observed survival in the placebo group was longer than what was predicted by the two natural history cohorts, discounted them. When you think about it, they were on placebo through the double-blind period, but the majority did go on to drug in the open label; so they're not in that sense a pure placebo group, so they have an intermediate survival and in some ways makes sense to me.

I did ask a question to the sponsor; when you look at the subjects who never went into the open label, who are initially randomized to placebo, their survival seemed to be closer to the prediction. So it will be interesting to hear what other members think, or maybe I'm thinking about it the wrong way. But it seemed to me that the difference between the natural history predictions and the survival on the placebo can't be explained in a way that doesn't discount those analyses. Thanks.

DR. MONTINE: Thank you.

DR. NATH: Jeff, this is Avi. Thanks for that explanation. I appreciate that. Thanks.

DR. MONTINE: Thank you, Avi.

So effectiveness, if we could focus our comments on how today's new information has moved you, one way or the other, on effectiveness.

DR. TRAYNOR: This is Bryan Traynor here. I would say that it's mildly to moderately persuasive. The issue that comes up with looking at the natural history data is what's the source of that natural history data.

Simply, we pretty much as epidemiologists in ALS kind of recognize that the gold standard is really the population-based registries that are available, particularly in Europe. Now some of them were part of that ENCALS efforts, so the Irish and the various Italian databases were part of that. I think even the English one was as well, although there was other data thrown in there as well. But that data is probably as close to population base as you're going to get in the ALS

world.

I'm not so much impressed by numbers, but that really is not the issue when it comes to ALS. It's more the source of the data and the population base. So I'd say I'm mildly to moderately persuaded by that. At least it's better than what it was in March.

DR. MONTINE: Great. Thank you, Dr. Traynor; very helpful.

I'll just go down the list as I see it.

Dr. Caleb Alexander, your hand is up.

DR. C. ALEXANDER: Yes. Can you hear me?

DR. MONTINE: I can.

DR. C. ALEXANDER: Great. Yes. I think the natural history data is very interesting. I was a little surprised that the sponsor didn't suggest it as the primary confirmatory evidence of efficacy, although I'm sure they have their reasons guided by the FDA to suggest that the open-label data is the primary confirmatory evidence. But the issue with the natural history data is not just the source of the information, but it's how it's analyzed, and

how those analyses are put together.

I think what we heard from the FDA is that, typically -- there was a very good question from one of you, which was a question that I was going to ask myself, which was in what settings is natural history data, or what the FDA calls, quote/unquote, "well-documented natural history of disease studies," in what settings would that suffice as confirmatory evidence? And what we heard from the FDA was that it's in settings where it is prespecified and where there is a great deal of work, a priori, between the FDA and the sponsor to design and execute those studies.

History is rife with examples of natural history studies that have gone sideways and that have not alternately borne out, so I think that the selection of external controls and the use of natural history studies as a basis for that is one which requires an extraordinary amount of caution. And that's the reason that we heard the FDA's perspective, that in settings where they believe -- I don't want to misquote them, but

essentially that in settings where it's used as confirmatory evidence, that it's prespecified, and those analytic plans are carefully developed between the sponsor and the FDA; not after the fact, but in advance, in advance of the studies being underway.

DR. MONTINE: Great. Thank you. So you find it less persuasive. I don't mean to put words in your mouth, but just summarizing for me.

Dr. Fischbeck, your feelings, your thinking or perspective.

DR. FISCHBECK: Yes. There's more analysis and some more data that was presented today, but it has not for me reached the level of substantial evidence of effectiveness that we need to approve it, or the FDA needs to -- or encourage them to approve it.

Just to touch briefly again on Dr. Traynor's earlier point about cost, it's true that we're not supposed to be talking about how much it cost, and I did ask last time, and the CEO of the company didn't answer or refused to answer. He said,

"Well, we have to figure it out later."

But what we are basically doing, as I understand it, is helping to decide whether or not the company can charge for this drug between now and the end of phase 3, or perhaps longer, and I don't think it's met the standard of evidence to allow them to sell the drug. I don't think there's any limit on their ability to give it away for free. They can do that by expanding their expanded access program or by opening phase 3 in the U.S. They already had the sites identified and started enrolling patients, so that would give ALS patients the opportunity to participate in the trial in this country. I think they should move in that direction rather than pushing us further to approve it for sale.

DR. MONTINE: Thank you so much for your comments.

Dr. Apostolova, your hand is up.

DR. APOSTOLOVA: Okay. Can you guys hear me?

DR. MONTINE: I can.

DR. APOSTOLOVA: Oh, good.

Yes, it's interesting that people bring the question of cost. I come from the Alzheimer's world where it's a very common disorder that goes on for 10-15 years, so the ramification of a costly drug for the treatment of Alzheimer's is huge. ALS is a rare disease. Survival is a couple of years or three, so I don't know that I would factor in cost as much.

On the other hand, has the data persuaded me? Mildly to modestly. I've been reassured by seeing two external control samples with all the [indiscernible] mentioned by the FDA statisticians that they still find are prolonged survival. So it's unidirectional. There is no -- to me, that is some confirmation of effect, and to deprive ALS patients from a drug that might work, it's probably not something I would feel terribly comfortable with my conscience, to say.

In the previous meeting, it wasn't that clear. It's still questionable, but, yes, I would say cost for a rare disease with such a harsh

prognosis, I don't know if I'll go there.

DR. MONTINE: Thank you, Liana. That's very helpful.

Mr. Weston, you have your hand up.

MR. WESTON: Yes. Thanks. A couple of thoughts comparing the information we had to consider for this meeting against what we saw in March, I was a little disappointed at the lack of more persuasive confirmatory analysis. I was hoping for something more. I voted in favor of this the last time because I felt, on balance, it made sense from a patient representative perspective.

I'm not a statistician. I'm not a practicing physician, but I can't decouple my thoughts about that from my thoughts about the unmet need and where this drug is going in trial, so I won't be changing my vote for those reasons.

But also on the topic of cost, I don't know if anybody's looked at the fact that oral edaravone, at least on my insurance formulary, is ridiculously expensive. I wouldn't take it. It

just cost way too much, yet that's fully approved, and there wasn't a lot of discussion about that. Bang. It's on the market, so they can charge for it. And that's a whole different meeting, I think, is the way in which our corporate medical world is regulated and how profit is a motivation, a necessary motivation. But back to the question, I'm equally maybe a little bit more persuaded that this is a drug that we should recommend approval of to the FDA.

DR. MONTINE: Thank you, Mr. Weston.

We're running short on time, so just to be fair, my own opinion is I agree with Liana and others who have said that what we were shown today, although still has its limitations and challenges, it's all trending in the same direction. So it has pushed me further along in my assessment of its effectiveness. Then, of course, as Mr. Weston and others have eloquently reminded us, we need to consider the urgent need for new therapeutics in this area.

I'm not entirely sure. Liana and Mark

Weston, your hands are up, but I imagine that's because you just spoke. Yes.

Liana, do you have another -- no. Okay. Thank you.

We now move on to the next question, which is a voting question. Dr. Jessica Seo will provide the instructions for the voting.

DR. SEO: Thank you, Dr. Montine. I apologize. I just wanted to relay to you, before we get to the voting, that there were some requests from the FDA and sponsor to speak, for your consideration, to grant their requests --

DR. MONTINE: No, of course. I'm sorry.

DR. SEO: -- if you feel it's relevant to a discussion.

DR. MONTINE: Of course. I'm sorry. I didn't see the comments in the chat.

Dr. Buracchio, please.

DR. BURACCHIO: Hi. This is Teresa Buracchio. I just wanted to provide some additional clarification on a comment that I made earlier in response to a question regarding the

ability of externally-controlled data to serve as confirmatory evidence. I did state that, ideally, such data would be prespecified and discussed with the agency prior to doing the analyses. I think that is an ideal situation but often may not be feasible.

So I do want to just note that confirmatory evidence can be just about anything. I gave some examples on one of the slides from our guidances of what confirmatory evidence could be, and I think natural history data was listed as one of those things on there that was intended to support particularly persuasive results.

But I think if we did have natural history data as a comparison, and we did have very compelling results that were able to overcome many of the biases that are inherent to those types of analyses, that we would be willing to consider those for confirmatory evidence even if the sponsor had not had the opportunity to discuss those with the agency beforehand.

So I just wanted to clarify that point, and

I'll ask Dr. Dunn if he had anything he wanted to add to that comment.

DR. DUNN: Thanks, Dr. Buracchio.

This is Dr. Dunn. No, nothing specific to add, other than to support your portrayal of the situation. It's certainly true that when sponsors want to work with us in difficult situations to use an external control as kind of a primary basis for assessing an outcome, a primary outcome in a prespecified way, then a lot of that rigorous, prospective discussion is going to occur because, as Dr. Buracchio said, it's not even that uncommon to interrogate external databases of sufficient quality to try to get a sense about how things are going after a study may have been performed.

Of course that's not the same as using those data for a primary outcome in a prespecified way, but its ability to serve as confirmatory evidence is as Dr. Buracchio described, and there's no need to identify any one particular thing as the confirmatory evidence. There's obviously a variety of related pieces of data that are being

entertained here for confirmatory evidence, as Dr. Buracchio said; but nothing to add, other than just to support your comments, Dr. Buracchio. Thank you.

DR. MONTINE: Thank you both.

I understand that our colleagues from Amylyx would like to make a comment. That's fine. I just would please ask to be brief. We're running short on remaining time allotted. Please.

DR. TIMMONS: Yes. Hello. This is Dr. Timmons. I'll be very brief. We're actually on the same wavelength as the FDA. We found a publication that summarized 45 drug approvals from 2000 to 2019 that used external controls in their approval. Forty-four percent of those came from historical controls that were derived retrospectively, as showed today. So we just wanted to share that information. Thank you.

DR. MONTINE: Thank you. Okay. So I'll try this again.

We will now move on to the next question, which is a voting question. Dr. Jessica Seo will

provide the instructions for the voting.

DR. SEO: Thank you, Dr. Montine.

Question 2 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. There will be no discussion in the breakout room. You should select the radio button that is the round circular button in the window 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 closed. 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 to; however, you should also address any subparts of the voting question, if there are any.

Are there any questions about the voting process before we begin?

DR. C. ALEXANDER: Well, this is Caleb Alexander. I have a question about the question itself.

DR. SEO: I believe Dr. Montine will go ahead and read the question into the record and ask for any questions about the voting.

DR. C. ALEXANDER: That's fine.

DR. SEO: Dr. Montine?

DR. MONTINE: Thank you.

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

Are there any questions or comments about the voting question?

Dr. Caleb Alexander?

DR. C. ALEXANDER: Yes. This is Caleb Alexander. Previously we were asked whether the data established a conclusion that the product is effective, and now we're being asked whether there is available evidence sufficient to support approval.

Are either of these asking whether we believe there's substantial evidence of effectiveness, or let me be more pointed and direct

and ask, are we currently being asked in this question whether there is substantial evidence of effectiveness? Are we being asked if the evidence today fulfills, meets, or exceeds the regulatory and statutory requirements for approval?

DR. MONTINE: Dr. --

DR. BURACCHIO: Hi. This is Teresa Buracchio.

(Crosstalk.)

DR. BURACCHIO: If I can start.

I was going to say that, in essence, I think we are asking about substantial evidence of effectiveness without using that language specifically. We were trying to use language that basically gets at the idea of substantial evidence of effectiveness, but we didn't want to use regulatory too much in the language. We were trying to make it, a little, plain language.

Dr. Dunn, did you want to add anything to that?

(Crosstalk.)

DR. C. ALEXANDER: But that is what you're

asking, just to be clear. I'm sorry. That is what you're asking, just to be clear, is whether the data provides substantial evidence of effectiveness, as you nicely defined it and explained it in the briefing materials today.

DR. BURACCHIO: Yes, that is correct.

DR. DUNN: This is Dr. Dunn. I'll jump in if I could.

DR. C. ALEXANDER: Okay.

DR. DUNN: Dr. Buracchio, is that alright if I jump in.

DR. BURACCHIO: Yes. Please do.

DR. DUNN: Right.

So it's an important question, and we certainly are asking a different question here. We've attempted to provide the committee with the relevant information that speaks to the need to make a scientific and regulatory decision, and we've attempted to provide the committee with the background information on pathways to approval, and for the requirements of that.

We recognize that the committee are not

regulators, and we also recognize, as we have explained to the committee, a conclusion about the existence of substantial evidence of effectiveness is a regulatory decision that we as regulators must make, and it's a qualitative decision. It's a subjective decision that, as we read to you from regulations, requires the exercise of scientific judgment.

So we have attempted to provide the committee with that background for you to give us your opinion about whether or not the evidence that you have heard supports approval. That's our question to the committee.

Dr. Montine, I hope that helps. Sorry to take up that extra time there.

DR. MONTINE: Oh, it's no problem at all, Dr. Dunn. Please, take whatever time you need. It's a critical question.

Thank you, Dr. Alexander, for clarifying.

Are there any other comments or questions about this question?

(No response.)

DR. MONTINE: Hearing none; then if there are no further questions or comments concerning the wording of the question, we will now begin voting on question 2.

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: 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. I will read the vote totals into the record. The chairperson will then 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 7 yeses, 2 noes, and zero abstentions.

Dr. Montine?

DR. MONTINE: Thank you.

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 to.

We'll start with the top of the list, Dr. Nath.

DR. NATH: Thank you, Dr. Montine.

I voted yes, and I had voted yes previously also, and I didn't see any reason to change that vote. But the presentation by the company, the analysis by the FDA was a very in-depth analysis the last time, and again this time, as well as the criteria presented to us. The discussion was very, very helpful in helping me make a decision. Last time I was on the fence and wasn't really sure which way to go, but this time it helped me move a little bit more towards the yes vote. Thank you. Over.

DR. MONTINE: Thank you.

Dr. Traynor?

DR. TRAYNOR: Hello. Hi. Can you hear me?

DR. MONTINE: I can.

DR. TRAYNOR: Good. This is Bryan Traynor. I voted yes, and I based my decision on a number of factors, which I'm going to outline now.

First and foremost, obviously the seriousness of the disease and the unmet need for treatment, but more relevant to what was discussed today, I think that the provision of the new information was supportive; albeit, a little bit exploratory, but it's still supportive in its overall nature.

I was also struck by the public statement of the CEO on behalf of the company, convincing them to voluntarily withdraw the drug if the phase 3 is negative, and in addition, the existence of an established method for the FDA to withdraw it if need be if that voluntary method doesn't actually work.

So on balance, I think the danger of delaying treatment by 3 years kind of overcomes, in a pretty robust way, the relatively real risk of a

false positive result for the phase 3. But I think that now, at this stage, we have to approve it, and wait and see what the actual results of the phase 3 is down the line. Thank you

DR. MONTINE: Thank you.

Dr. Follmann, please?

DR. FOLLMANN: Yes. Thank you. My name is Dean Follmann. I voted yes. I voted yes in March, and I thought that the evidence today was fairly similar to what we voted on in March. I think there was a better estimate of the survival benefit presented, but the totality of evidence, I thought the information content was similar to March.

What I did find different was, the updates, a thoughtful and thorough discussion about the evidentiary basis for approval, and I think that helped me to some extent, and I think it helped the other board members, the committee members as well, so I appreciate that discussion that they did. Over.

DR. MONTINE: Thank you.

Dr. Caleb Alexander?

DR. C. ALEXANDER: Thank you. I voted no. First, I do want to thank the sponsor and trial participants, and their loved ones, and the FDA, and all the parties that have come together and are working to develop new treatments for this disease.

I did vote no. As a husband, and father, and son, and clinician, I don't doubt for a minute the value of additional days or months of life, nor the willingness of many patients, many in the ALS community, to take upon the risks that this product doesn't work. But I voted no last time and, unfortunately, I don't believe the new evidence that we've reviewed, while promising, constitutes -- combined with that prior evidence -- substantial evidence of effectiveness.

We essentially have a single study with many non-trivial scientific concerns, confirmatory evidence that's not prespecified derived from the same study, and post hoc natural history analyses that we've heard about. In most cases where a single study may be used for approval, it's because the second trial is impracticable or unethical, and

here not only is another trial feasible, it's actually underway.

I also think the FDA, with all due respect, significantly understates the complexity and likelihood of their pulling a product from the market. Frankly, I'm not sure it's ever taken place, although admittedly in rare cases, manufacturers themselves have made the decision to do so. But regardless, as we heard from the FDA, whether or not they can ultimately pull a product from the market, it's no substitute for the evidentiary thresholds that are required for market access.

So again, I want to thank the parties involved working to develop new products for ALS, and I'm just as much looking forward to the results of the PHOENIX trial as anybody else. Thank you.

DR. MONTINE: Thank you.

Dr. Fischbeck, please?

DR. FISCHBECK: I agree with Dr. Alexander, Dr. Caleb Alexander. I'm impressed with all that was presented today by the company and by the FDA,

and really moved by the comments, all 1288 comments that were submitted. I didn't read them all, but I read enough to get the sense of burden that these families and patients are facing, and I'm well aware of that from having cared for ALS patients over the course of my career.

I do not think, though, that there is substantial evidence of effectiveness at this point. As Dr. Alexander said, there were some problems with the study in terms of the randomization, for example. The additional data is useful, but it's post hoc and not prespecified, the analysis that was used, which is kind of like trying to change the result of an athletic game, or I hesitate to say, an election, after the fact, after the trial is finished.

So I don't think that it's quite met the standard that we should have here to move forward with giving approval to the company before we have the results of phase 3. I do look forward to phase 3, and I appreciate the company's expanded access program, and I hope that we get the results

expeditiously and move on with a safe and effective treatment.

DR. MONTINE: Thank you.

Dr. Apostolova?

DR. APOSTOLOVA: Yes. I voted yes. I was previously a nay voter, and today's meeting, first and foremost, of course we need to take into account the disease that is being investigated, ALS. It's a horrific disorder. It's a death sentence. And very similar to the March 30 meeting, again, today, we have to have an internal dialogue between our scientific scrutiny and clinical compassion.

However, today I also saw there's now additional confirmatory evidence, which is not unequivocally persuasive, but nonetheless, it's quite reassuring, and because of that, I am voting in support of AMX0035.

DR. MONTINE: Thank you.

Mr. Weston?

MR. WESTON: Yes. Thank you. Just a couple of additional comments beyond those that I made

prior to the vote, for the record, this is Mark Weston, and I did vote in favor.

A lot of it has to do with the ok support for the previously presented data back in March, but also, my people, my community, they are willing to risk their lives by seeking out sometimes wildly expensive treatments that can be deadly or dangerous, and others of us hope to be able to access the expanded access programs for experimental drugs. But the trouble with that is that not every person with ALS has access to a multidisciplinary clinic, and then to further narrow that choice, not every clinic has an expanded access program. They're really expensive to operate, a lot of monitoring, a lot of reporting, and many very good neurologists work in hospitals, and offices, and clinics, where they simply don't have the bandwidth to do that, so it's very, very exclusionary.

As others have said, even if this drug, if it gets approved, doesn't work as desired, we live in a pretty competitive society, and people just

won't take it if it doesn't -- word gets around, and surviving people with ALS aren't going to take it. The FDA has grounds to withdraw it. Whether or not they would do it, I agree that's maybe a remote possibility, but they could do it. And I'd rather see people have access to this drug by a prescription, and maybe even through insurance carriers, and even less likely at an affordable price; but maybe we can keep our fingers crossed on that.

Those are some of the random reasons why I voted the same way that I voted on March 30th, which is to recommend to the FDA that it get off the fence, forthwith, and approve this. Thank you very much.

DR. MONTINE: Thank you, Mr. Weston.

Dr. Alexander, Robert Alexander?

DR. R. ALEXANDER: Yes. This is Robert Alexander, and I voted yes. I want to say that I really appreciate the testimony of the many ALS patients and their families, and just like last time, it really underlies the seriousness of ALS

and the profound unmet medical need.

It was a close call last time, so it does represent a change from my March vote. But I felt that there was now additional evidence to believe that there is a survival benefit associated with the drug, and that in my mind was sufficient for me to change my vote. Thanks.

DR. MONTINE: Thank you.

For the record, my name is Thomas Montine. I voted yes. My justification, or just for background, I voted no the last time. What I found especially helpful in today's discussion was the reviews by Dr. Dunn and Buracchio on judging what substantial evidence is within context, and setting that context with the ongoing phase 3 trial, the seriousness of the disease, the unmet medical need, the moving testimony of patients and families, and the consistent testimony of experts in treating patients with ALS. Although there are still limitations, in aggregate, my judgment was for, yes, to support.

I'd like to thank everyone for their time,

thoughtfulness, and effort into what was a very informative day. I'd like to thank our colleagues from Amylyx, of course our colleagues from the FDA, all of our presenters in the open session, especially patients and their loved ones. I think we've had a robust discussion that reflects the difficulty of this decision, and I know I speak for all of us in thanking the FDA for inviting our input.

Before we adjourn, Dr. Dunn, or any of our colleagues from the FDA, would you like to make a comment?

DR. DUNN: Sure, Dr. Montine. This is Dr. Dunn. Thank you for offering me the chance to say thank you. We're just a few minutes over time, and I appreciate your very well-managed handling of a difficult schedule today. I'll keep it brief since we are over time.

I simply want to echo what you just said, Dr. Montine, in your thanks that are offered to the patients and their loved ones, and also to so many who are invested more broadly in the ALS community,

who took their time and effort to address the committee, either directly today or in the extensive written comments, as we heard about from the committee members. That represents a lot of effort, and we take that very seriously. We keep these issues in mind at all times, and we're deeply, deeply appreciative of that input.

I very much want to thank the committee members as well. As we said at the beginning of the meeting, and reiterated throughout the day, we thought it was imperative that this committee have the opportunity -- given the sophisticated discussions that occurred during the first meeting and the supplementary material that the sponsor brought to our attention, we thought it was imperative that the committee have an opportunity to fully contemplate those data and give every aspect of the application their full consideration. We know that represented additional work for you. We know that's not easy, and you take time away from your normal workflow to do that on behalf of the American public.

We are deeply appreciative for the advice that you have provided us. As always, and as we say at the beginning, it is valuable and helpful to us, and we will continue to digest what we have heard from you as we continue and complete our review of the product. The most important thing is to simply say thank you.

Dr. Montine?

Adjournment

DR. MONTINE: Well, thank you, Dr. Dunn, and thank you, Dr. Seo and the entire team who organized today, and of course everyone who presented, thank you. I will now adjourn the meeting. Best to all.

(Whereupon, at 6:41 p.m., the meeting was adjourned.)