FOOD AND DRUG ADMINISTRATION

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

Virtual Meeting

Wednesday, March 22, 2023

9:15 a.m. to 5:31 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)

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

Richard J. Kryscio, PhD
Professor, Statistics and Biostatistics
University of Kentucky
Sanders-Brown Center on Aging, Room 230
Lexington, Kentucky

Michelle M. Mielke, PhD

Chair, Department of Epidemiology and Prevention
Professor of Epidemiology and Gerontology and Geriatric Medicine
Wake Forest University School of Medicine
Division of Public Health Sciences
Winston-Salem, North Carolina

Thomas J. Montine, MD, PhD

(Chairperson)
Chair, Department of Pathology
Stanford Medicine Endowed Professor
Stanford University School of Medicine
Stanford, California

PERIPHERAL AND CENTRAL NERVOUS SYSTEM DRUGS ADVISORY COMMITTEE MEMBER (Non-Voting)

Michael Gold, MS, MD

(Industry Representative)
Chief Medical Officer
Neumora Therapeutics
Watertown, Massachusetts

TEMPORARY MEMBERS (Voting)

Klaus Romero, MD, MS, FCP

Chief Science Officer

Critical Path Institute

Tucson, Arizona

Tanya Simuni, MD, FAAN

Professor of Neurology

Division Head, Parkinson's Disease and Movement Disorders Center

Northwestern University Feinberg School of Medicine

Chicago, Illinois

David Weisman, MD

Director, ANA Clinical Research Center.

Abington Neurologic Associates

Abington, Pennsylvania

Michael Wilson

(Patient Representative)

Oklahoma City, Oklahoma

FDA PARTICIPANTS (Non-Voting)

Teresa Buracchio, MD

Director (Acting)

Office of Neuroscience (ON)

Office of New Drugs (OND), CDER, FDA

Emily Freilich, MD

Cross-Discipline Team Lead

Deputy Director (Acting)

Division of Neurology 1 (DN 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

(9:15 a.m.)

Call to Order

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

As said, my name is Thomas Montine. I'll be chairing today's meeting. I will now call the March 22, 2023 meeting of the Peripheral and Central Nervous System Drugs Advisory Committee to order. Dr. Jessica Seo is our designated federal official through this meeting and will begin with introductions.

Introduction of Committee

DR. SEO: Good morning. 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 affiliation. We'll begin with our PCNS members,

starting with Dr. Robert Alexander.

DR. ALEXANDER: Good morning. This is Robert Alexander. I'm the chief scientific officer at the Alzheimer's Prevention Initiative at the Banner Alzheimer's Institute and a research professor at the University of Arizona College of Medicine in Phoenix. Thank you.

DR. SEO: Thank you. Next is Dr. Apostolova.

DR. APOSTOLOVA: Hello. I'm Liana Apostolova. I am distinguished professor at Indiana University and professor of neurology, with experience in neurodegenerative diseases, specifically Alzheimer's disease.

DR. SEO: Thank you.

I believe we're still getting Dr. Gold connected, so we'll come back to him.

We'll move on to Dr. Kryscio.

DR. KRYSCIO: Good morning. It's Richard Kryscio. I'm professor of statistics and biostatistics at the University of Kentucky.

DR. SEO: Thank you.

Dr. Mielke?

DR. MIELKE: Good morning. Michelle. Mielke. I'm chair of the Department of Epidemiology and Prevention, professor of epidemiology, and also gerontology and geriatric medicine at Wake Forest University School of Medicine.

DR. SEO: Thank you.

Dr. Montine?

DR. MONTINE: Good morning. My name is Tom Montine, professor and chair of the Department of Pathology at Stanford University.

DR. SEO: Thank you.

Next we have our temporary voting members. We'll begin with Dr. Romero.

DR. ROMERO: Hello, everybody. Klaus Romero here. I'm chief science officer for the Critical Path Institute. Thank you.

DR. SEO: Thank you.

Dr. Simuni?

DR. SIMUNI: Good morning. I'm Tanya Simuni. I'm professor of neurology at Northwestern

University, Chicago, with expertise in Parkinson's and other movement disorders/

DR. SEO: Thank you. Dr. Weisman?

DR. WEISMAN: Hi. My name's Dave Weisman, and I'm a neurologist and trialist concentrating in Alzheimer's disease, and I'm at Abington Neurologic.

DR. SEO: Thank you.

Mr. Wilson?

MR. WILSON: Yes. This is Michael Wilson. I'll be the patient representative for today. My ALS journey started about six years ago, and thank you for having me.

DR. SEO: Thank you.

We'll move on to our FDA participants, beginning with Dr. Buracchio.

DR. BURACCHIO: Hi. I'm Teresa Buracchio. I am the acting director for the Office of Neuroscience in CDER, FDA.

DR. SEO: Thank you.

And Dr. Freilich?

DR. FREILICH: Good morning. I'm Emily

Freilich. I'm the acting deputy director and cross-disciplinary team lead for the Division of Neurology 1.

DR. SEO: Thank you.

Back to you again, Dr. Montine.

DR. MONTINE: Thank you, everyone.

For topics such as those being discussed at this meeting, there are often a variety of opinions, some of which are quite strongly held. Our goal today 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.

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 the break. Thank you.

Jessica Seo will read the Conflict of Interest Statement for the meeting.

Conflict of Interest Statement

DR. SEO: Thank you, Dr. Montine.

The Food and Drug Administration, or FDA, is convening today's meeting of the Peripheral and Central Nervous System Drugs Advisory Committee under the authority of the Federal Advisory Committee Act, 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 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.C. 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.C. 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 discussion of new drug application, or NDA, 215887, for tofersen, BIIB067, intrathecal injection, submitted by Biogen, Incorporated, for the treatment of amyotrophic lateral sclerosis associated with a mutation in the superoxide dismutase 1, or SOD1, gene.

This is a particular matters meeting during which specific matters related to Biogen's NDA will be discussed. Based on the agenda for today's meeting and all financial interests reported by the committee members and temporary voting members, a conflict of interest waiver has been issued in

accordance with 18 U.S.C. Section 208(b)(3) to Dr. Robert C. Alexander. Dr. Alexander's waiver involves stock holdings in a competing firm. The waiver allows Dr. Alexander to participate fully in today's deliberations.

FDA's reason for issuing the waivers are described in the waiver documents, which are posted on FDA's website at www.fda.gov/advisory-committees/committees-and-meeting-materials/human-drug-advisory-committees. A copy of the waiver may also be obtained by submitting a written request to the agency's Freedom of Information Division at 5630 Fishers Lane, Room 1035, Rockville, Maryland, 20857, or requests may be sent via fax to 301-827-9267. 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'd like to disclose that Dr. Michael Gold is participating in this meeting as a non-voting industry representative acting on

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

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: Thank you.

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

FDA Introductory Comments - Teresa Buracchio

DR. BURACCHIO: Thank you, Dr. Montine.

Welcome to our committee members and guests

who are joining us for this important meeting. At today's meeting, we will discuss the application for tofersen for the treatment of patients with ALS associated with the SOD1 genetic mutation, which I will refer to as SOD1 ALS.

I would like to begin by thanking the committee for the time that they have taken to review the advance materials and for joining us today to discuss the topics that are under consideration for this application. Your perspectives and input are very valuable to the agency.

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

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

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

ALS, associated with a mutation in the SOD1 gene, has a similar clinical course for sporadic ALS. It is a progressive and fatal disease that causes loss of motor function that impacts the ability to walk, speak, swallow, and ultimately to breathe. The mechanism by which mutations in the SOD1 gene cause ALS are not fully understood, although it is postulated that the mutations may lead to a toxic accumulation of mutated or misfolded SOD1 protein.

ALS is a rare disease with an estimated prevalence of 15,[000] to 20,000 patients in the U.S., and the patients with the SOD1 mutation represent a very small subset of that population. It is estimated that the prevalence of SOD1 ALS in the U.S. is less than 500 patients. There are no therapies approved specifically for SOD1 ALS.

Tofersen is an antisense oligonucleotide, or ASO, that is designed to bind and degrade SOD1 mRNA to reduce synthesis and accumulation of SOD1 protein. Because tofersen reduces SOD1 protein translation, an event that is upstream of the pathological mechanisms implicated in SOD1 ALS, it is anticipated that any therapeutic benefit of tofersen would apply to all SOD1 ALS patients regardless of the mutation type.

I will now provide a brief overview of the data that we will be discussing today. The applicant conducted a 28-week randomized, double-blind, placebo-controlled pivotal study in 108 adult patients with SOD1 ALS. I note that this is a relatively large study considering the very

low prevalence of the disease. Randomization was stratified by categorization of patients as fast progressors and non-fast progressors. Fast progressors were defined by genetic mutation and pre-randomization slope on the ALSFRS-R, and this fast progressor group formed the primary analysis or modified intent-to-treat population.

The study included endpoints commonly used in ALS clinical trials such as the ALSFRS-R in assessment of clinical function and assessment of respiratory function, strength, and time to death or permanent ventilation. The study included some assessments of the biomarkers SOD1 protein in cerebrospinal fluid, and neurofilament light chain, or NfL, in plasma, which is a marker of axonal injury of neurons and neurodegeneration.

The study failed to show a statistically significant difference between the tofersen and placebo groups for the primary or secondary endpoints on the prespecified primary analysis. Although not statistically significant, there did appear to be some separation between the treatment

groups on clinical outcomes at week 28. Additionally, there were marked nominally significant reductions in SOD1 protein and NfL.

Following completion of the placebo-controlled study, all participants had the opportunity to enroll in an open-label extension study, where they received open-label tofersen treatment but remained blinded through the treatment received in a double-blind study. The primary objective of the extension study was to evaluate safety and tolerability, but the study provides additional biomarker and clinical endpoint data through week 52 and is still ongoing.

After switching to tofersen in the open-label extension, patients previously receiving placebo experienced a reduction in NfL after 24 weeks of treatment, similar to that observed in tofersen-treated patients in the double-blind study. There were also trends that showed increasing separation on primary and secondary clinical outcomes at week 52 that favorite patients who initially received tofersen in the double-blind

study compared to those with a delayed start in the extension study.

The division met with the applicant in formal meetings in December 2021 and again in April 2022, and reviewed the study results. The division was open to the submission of an NDA to review the available data and whether it could support a treatment benefit given the context of the seriousness and rarity of SOD1 ALS and the substantial unmet need.

The applicant submitted an NDA on May 25, 2022, seeking accelerated approval for the tofersen for the treatment of SOD1 ALS. As a reminder, accelerated approval is a particular type of approval that FDA may grant for a product for a serious or life-threatening disease upon the determination that the product has an effect on a surrogate endpoint that is reasonably likely to predict a clinical benefit based on epidemiologic, therapeutic, pathophysiologic, or other evidence. Approval is subject to the requirement that the applicant study the drug further to verify benefit.

This is a complex data set, and there are different approaches to analyzing and considering this data that you will hear today. Based on post hoc exploration of the unblinded Study 101C data, the applicant determined that the criteria used to define a fast progressor population were not appropriate and that baseline NfL was a more informative marker for identifying a faster progressing population. Therefore, they revised their statistical analysis plan for the open-label extension data to focus on a total randomized or intent-to-treat population and included NfL as a covariate.

When analyzed in that way, there are some clinical outcomes that reach nominal statistical significance at week 52, and those analyses will be presented by the applicant today. However, the FDA Office of Biostatistics review team feels that it is most appropriate to analyze the data using the initial prespecified analysis method, as those are not subject to bias from knowledge of the unblinded data. Our biostatistics reviewer, Tristan Massie,

will present analyses using that approach today. Using the prespecified approach, the analyses do not reach nominal statistical significance; however, notably, the reductions in both SOD1 protein and NfL appear robust no matter which analysis method is used.

It is also important to note that the post hoc exploratory analyses conducted by both the applicant and agency reviewers did identify limitations to Study 101C that may have contributed to the inability to detect a treatment effect for tofersen if there is one. Most notably, the decline in both the placebo and treatment groups was much less than expected, leading to the study being greatly underpowered.

Additionally, the study duration of 28 weeks may not have been sufficient to observe a treatment benefit based on the mechanism of the drug. The purpose of noting these limitations in the study design is not to try to explain away a negative study or turn it into a positive study. Study 101C is clearly a negative study; however, the agency

considers that the data appear to suggest a treatment effect of tofersen in SOD1 ALS.

You will hear today that there is convincing reduction on NfL and there are consistent trends on clinical outcomes that favor tofersen, even if they do not reach statistical significance. If there is a treatment effect of tofersen, it is important to understand why Study 101C may have failed to detect this effect.

I will also note that the analyses of the extension study are considered exploratory analyses, as they were conducted after Study 101C was unblinded. In a typical drug development program for more prevalent disease, such analyses would be considered hypothesis generating, and the agency would typically require additional studies to confirm those hypotheses, such as an additional study stratified by baseline NfL levels and with a longer duration. However, SOD1 ALS is an exceptionally rare disease, and it would be very challenging to conduct a second study in the same symptomatic population at the current time, and

such a study would likely take several years if it could be conducted. Therefore, given this context, the agency feels that it is critical we consider all the available data in our assessment of tofersen for SOD1 ALS, including exploratory analyses, as they are supported by a strong scientific rationale.

Although the reductions in NfL appear convincing, it is necessary to consider whether those reductions in NfL, in the context of a targeted therapy that lowers SOD1 protein in SOD1 ALS, can be considered reasonably likely to predict a clinical benefit.

Reviewers from our Office of Biostatistics and Office of Clinical Pharmacology will provide different perspectives on the assessment of NfL as a reasonably likely surrogate endpoint. Our biostatistics reviewers will discuss limitations of using the clinical data from a negative study to inform the reasonably likely standard, and our clinical pharmacology reviewers will discuss the pathophysiologic and epidemiologic evidence, as

well as the data from the current study that support NfL as a surrogate endpoint that is reasonably likely to predict clinical benefit.

Although it is not the topic of a specific presentation today, the agency will ask the committee members to consider if all the available data presented today establishes, rather than just predicts, a treatment benefit of tofersen in SOD1 ALS that could support full approval of the drug.

I will now give a brief discussion of regulatory flexibility. The statutory standards for substantial evidence of effectiveness apply to drugs developed for ALS just as the standards apply for all drug development. However, FDA recognizes that it may be appropriate to exercise regulatory flexibility in applying the statutory standards to drugs intended to treat serious diseases with unmet medical needs while preserving the appropriate assurance of safety and effectiveness. Our regulations allow for and encourage such use of regulatory flexibility, especially where no satisfactory alternative therapy exists.

The 2019 Draft Guidance, "Demonstrating Substantial Evidence of Effectiveness for Human Drug and Biological Products," also discusses 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 need.

The guidance states that, "In certain settings, a somewhat greater risk, compared to placebo-controlled or other randomized superiority trials, 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."

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

Given these considerations, we seek the input from the advisory committee on the strength of the efficacy data to support a potential treatment benefit of tofersen in SOD1 ALS in two scenarios. The first scenario would invoke the accelerated approval pathway, which allows approval of a drug based on an effect on a surrogate endpoint that is found to be reasonably likely to predict clinical benefit. The surrogate endpoint serves as an indirect measure of clinical benefit, and under this pathway, confirmation of the clinical benefit is required.

In this situation, we are considering whether the available evidence supports that the reduction in NfL observed in tofersen-treated patients with SOD1 ALS is reasonably likely to predict clinical benefit for those patients. The second scenario considers whether the available data is strong enough in this rare disease population that clinical trends that suggest benefit in the open-label expansion at week 52 may

be sufficient, combined with confirmatory evidence of reduction in SOD1 and NfL to establish a treatment benefit of SOD1 ALS to support full approval of the drug.

This brings us to the question that you will be asked to vote on today. You will also be asked to discuss the data that support each question prior to voting, and you will be asked to consider benefit-risk considerations as well. In all of your discussions today, we ask that you keep in mind the context that SOD1 ALS is a serious and very rare disease with a substantial unmet need.

Following my remarks, you will hear presentations from the applicant's team, and you will have a chance to ask clarifying questions. After a short break for lunch, we will reconvene with presentations from the FDA from Dr. Emily Freilich, the acting deputy director and cross-discipline team leader for this application in the Division of Neurology 1; Dr. Tristan Massie, a reviewer with the Office of Biostatistics; and Drs. Vishnu Sharma and Xiaohan Cai, reviewers from

the Office of Clinical Pharmacology. You will again have a chance to ask clarifying questions.

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

Dr. Montine, thank you for the time to offer my comments, and I return the proceedings to you.

DR. MONTINE: Thank you, Dr. Buracchio.

DR. SEO: Dr. Montine --

DR. MONTINE: Yes?

DR. SEO: -- this is Jessica speaking. I apologize for the interruption. We have been able to get Dr. Gold connected.

Dr. Gold, if you could take this moment to introduce yourself into the record by stating your

name and affiliation, please?

DR. GOLD: Can you hear me ok?

DR. SEO: Yes, we hear you well.

DR. GOLD: Great. This is Michael Gold. I'm the non-voting industry representative. I am the chief medical officer at Neumora Therapeutics.

DR. SEO: Thank you, Dr. Gold.

I'll hand it back to you, Dr. Montine, to introduce the applicant presentation.

DR. MONTINE: Thank you, Dr. Seo, and thank you again, Dr. Buracchio, for a very clear, concise presentation of the issues.

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 applicant, 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 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 the presentations from Biogen.

Applicant Presentation – Toby Ferguson

DR. FERGUSON: Good morning. My name is Toby Ferguson. I lead the Neuromuscular Development Unit at Biogen. Today I'll provide introductory remarks on the tofersen development program.

The proposed indication for tofersen is for the treatment of adults with amyotrophic lateral

sclerosis associated with a mutation in the superoxide 1 dismutase gene. ALS is a rare neurological disease characterized by loss of motor neurons in the brain and spinal cord. Prevalence of ALS in the United States is approximately 18,000 cases, well below the defined criteria for orphan disease status. SOD1 ALS is even more rare. It represents approximately 2 percent of the overall ALS population with an estimated 330 individuals living with SOD1 ALS in the United States.

Although disease progression can vary substantially, SOD1 ALS is always fatal. Median survival is estimated at 2.7 years from diagnosis with substantially shorter survival seen in the more rapidly progressive forms of the disease. Today in the United States, there are three approved therapies for the treatment of ALS. Despite these therapies, there remains a substantial unmet need in all ALS, and no approved therapies that target SOD1 pathophysiology.

Scientific evidence strongly suggests that

mutant SOD1 protein is toxic to the nervous system, therefore, reduction of SOD1 protein in people with SOD1 ALS may be an effective therapy. The first is an antisense oligonucleotide designed to facilitate the degradation of SOD1 mRNA, and therefore reduce synthesis of SOD1 protein. Reducing synthesis of new SOD1 protein would prevent further accumulation of new toxic SOD1 and allow endogenous mechanisms to remove existing toxic SOD1.

By reducing the amount of toxic SOD1 protein, tofersen would be predicted to preserve motor neuron integrity. One method to assess motor neuron integrity would be measurement of neurofilament light chain, as it is a key component of neurons that leak into the blood and CSF during neurodegeneration. Thus, the mechanism of tofersen is intended to treat the underlying cause of SOD1 ALS, and tofersen treatment would be predicted to slow the neurodegenerative process.

The primary first study for tofersen was Study 101. This study had three parts of which part C, VALOR, was a pivotal portion of the study.

VALOR was designed to demonstrate substantial evidence of effectiveness based on changing clinical function as measured by the Revised ALS Function Rating Scale at 6 months. Key secondary endpoints included CSF SOD1 and plasma neurofilament light.

VALOR randomized 108 participants, a sizable number given the rarity of SOD1 ALS. VALOR was supported by an open-label extension study, Study 102, which is prospectively designed to determine if early-start treatment of tofersen could provide benefit over late-start tofersen treatment. Additionally, tofersen is being investigated in presymptomatic SOD1 carriers in the phase 3 study, ATLAS. The ATLAS study is an ongoing, placebo-controlled study that could potentially serve as a confirmatory study should tofersen receive accelerated approval.

VALOR began in 2019, and had the week 28 readout in August 2021. Importantly, VALOR did not achieve statistical significance on the primary endpoint, change in ALS function; however,

substantial reductions were observed in CSF SOD1, a mark of target engagement, and neurofilament, a mark of neurodegeneration. Since the design and initiation of VALOR, the scientific community has made great strides in understanding the importance of neurofilament ALS, including as a predictor of disease progression and mortality. Furthermore, the integration of VALOR and the open-label extension allowed for the observation of tofersen's effects over longer periods of time. These integrated analyses, though exploratory, observed that early treatment with tofersen led to better outcomes on multiple measures.

Biogen had three formal type B and Type C meetings with the FDA to test the VALOR data set, its open-label extension, and the feasibility of neurofilament as a surrogate endpoint suitable for accelerated approval. The NDA was submitted for accelerated approval and was accepted for product review in July of 2022. Of note, VALOR and open-label extension results were published in the New England Journal of Medicine September of last

year.

As explained in the FDA's briefing book and under the FDA guidance for expedited programs for serious conditions, the FDA may grant an accelerated approval to a product for a serious or life-threatening condition that has an effect on a surrogate endpoint that is reasonably likely to predict clinical benefit, while taking into account the severity and rarity of the condition and lack of alternative treatments.

To determine whether an endpoint is reasonably likely to be a clinical benefit is ultimately a matter of judgment that depends on the biological plausibility of the relationship between the disease, the endpoint, and the desired effect, and the empirical evidence to support that relationship. It is important to note that a surrogate endpoint that is reasonably likely to predict clinical benefit does not yet have sufficient evidence to be considered a validated surrogate endpoint, but they nonetheless support an accelerated approval.

The support for accelerated approval of tofersen is consistent with the FDA guidance on serious conditions I've just reviewed. Today you will hear that SOD1 ALS is a rare and life-threatening disease with critical unmet medical need; evidence that substantial reductions in neurofilament are reasonably likely to predict clinical benefit in people with SOD1 ALS; the efficacy and safety data of tofersen support benefit-risk in the context of neurofilament light reduction; and finally, Biogen's commitment to ongoing and long-term data generation plans for tofersen.

Now I would like to highlight our key speakers. Dr. Tim Miller will highlight the important disease background; Dr. Stephanie Fradette will review the tofersen efficacy data; Dr. Laura Fanning will discuss the safety of tofersen; Dr. Miller will return for discussion on his clinical perspective of tofersen; and Dr. Fradette will deliver Biogen's concluding remarks.

In addition, we have assembled a number of experts to help answer your additional questions you can see noted here. Thank you, and I would now like to turn it over to Dr. Miller

Applicant Presentation - Timothy Miller

DR. MILLER: Thank you, Dr. Ferguson.

Hello. My name is Tim Miller, and I am absolutely delighted to be a part of this discussion today. I'm a neurologist/neuroscientist at Washington University in St. Louis, and I've been working on SOD1 antisense oligos for the last 20 years. I'm a consultant for Biogen, as well as Ionis Pharmaceuticals, and I'm part of a licensing agreement with Ionis. Ionis Pharmaceuticals developed tofersen. I do not have any direct financial benefit based on the outcome of this meeting.

ALS, as many of you know, is a fatal, neurodegenerative disease. It is a relentlessly progressive, adult-onset disease characterized by weakness that leads to difficulty breathing, swallowing, moving limbs, and walking due to the

loss of motor neurons. ALS is fatal. Most people die from the failure of the respiratory muscles within 3 to 5 years from the beginning of the disease. Many of the submitted comments reinforce the monumental impact this disease has on individuals and their families, and I anticipate the open public hearing this afternoon will do so as well.

There are multiple mechanisms that have been applied for ALS, including glutamate toxicity, oxidative stress, neurofilament accumulation, and dysfunction of axonal transport. The cells besides the neurons are clearly involved, the microglia and the astrocyte. For most cases of ALS, we do not understand exactly what has caused the disease, but in some cases, we do understand; for example, in those with a genetic mutation.

ALS has traditionally been characterized as sporadic or familial with about 10 percent of cases being familial, but with more recent genetic discoveries and broader number of people getting genetic testing, it has become clear that some

without a known family history have an ALS causing mutation, and thus genetic cause of the disease. Though I may jump back to the term "sporadic" at times, those without a known family history are probably best referred to as a singleton. The genetic group would then include some singleton and some with a known family history.

Among the familial subset, there are a variety of mutations, and SOD1, shown here in blue, causes 10 to 20 percent of the familiar portion or 1 to 2 percent of all ALS. When running the numbers for the United States, we see that SOD1 ALS is estimated to affect approximately 300 to 350 people in the United States.

The mutation in the SOD1 gene resulted in abnormal SOD1 protein, which is misfolded, resulting in aggregates. The toxicity from the misfolded SOD1 is not clearly understood, though likely is related to the formation of aggregates, and despite not understanding fully this toxicity, a large amount of research demonstrates that there is a toxic gain of function. Based on this toxic

gain of function, reducing the level of SOD1 is predicted to be therapeutic.

SOD1 ALS is highly heterogeneous. Shown below are different disease mutations and the mean disease duration time from symptom onset. You can see that some of the mutations are typically associated with very aggressive disease, for example, A5V, while others have a relatively slow time course.

When I was a fellow in neuromuscular in 2002, I diagnosed a patient with SOD1 ALS, and paraphrasing that conversation, the person living with ALS said, "Well, now that you know exactly what is causing my ALS, what do you have designed to treat SOD1 ALS?" And unfortunately at that time, all we had was riluzole, and I explained to the person living with ALS that this was a drug that clearly prolonged the disease modestly, but neither you nor the people taking care of you would be able to tell that you are on this drug.

Now, 20 years later, we have made extensive progress in ALS therapeutics. Nuedexta has a major

effect on the symptoms of pseudobulbar affect, each of these other medications slows down disease, but modestly, and similar to my discussion 20 years ago, neither the participants nor the providers are able to see an effect of the drug. This contrasts with tofersen and is a point I will come back to in the clinical perspectives deck. In addition, none of these medications are designed to target the underlying disease or pathology of SOD1-related ALS. As will be described further today, tofersen is an SOD1 antisense oligonucleotide designed to target the underlying pathology of SOD1 ALS.

Tofersen is the name of this SOD1 antisense oligo. SOD1 was discovered to be related to ALS in 1993 by Bob Brown in collaboration with many others. In the early 2000s, we started working on antisense oligo development, and this shows the time line and the history of the development over the last 20 years. Some notable points are that the original SOD1 ASO trial was the first in-human for CSF delivery of an ASO for a neurologic disorder. The SOD1 ASO was redesigned, and a

newer, more potent, higher likelihood to be tolerable ASO was developed and named tofersen. The first tofersen trial was initiated in 2016 and the phase 3 trial published in the fall of 2022.

Antisense oligonucleotide are DNA like or RNA like chemicals that are modified at the backbone and modified at the 2-prime position. They're often about 20 mers. The modifications increase the binding to target RNA and increase the stability in biological fluid. The modifications also help to evade the immune system.

Antisense oligos do not cross the blood-brain barrier, and are thus delivered directly to the central nervous system via an intrathecal delivery to the cerebral spinal fluid, which then delivers the ASO broadly throughout the brain and spinal cord. Once the ASO has reached the cell, they're taken up into the cell by a mechanism that is still not completely understood, and inside the cell they get into the nucleus, and in the nucleus the antisense oligo binds to the target RNA.

This duplex is recognized by the enzyme RNase H. RNase H then degrades the target mRNA, and once the target mRNA is degraded, there's a decreased amount of protein produced, and thus the protein level falls according to the protein half-life. Tofersen is an antisense oligo design to degrade SOD1 mRNA, and thus reduce the protein synthesis. Note that tofersen will lower both mutant and wild-type SOD1 and will target all of the known SOD1 mutation.

Tofersen is targeting the initiating pathway causing ALS, so one way to understand or read out a drug like tofersen is to look at the effect on neurofilament. As I will show you in a large body of literature that will follow in the next set of slides, neurofilaments have been studied extensively in the setting of ALS.

Neurofilaments are intermediate filament proteins. These are part of the structures of axons. These intermediate filaments come in three different flavors, heavy medium, and light neurofilament. Heavy and light are the two that

have been studied the most in this setting of ALS, and I will show you some of these data. With axon injury, the neurofilaments are released from the cell, and then into the blood, and also into the cerebrospinal fluid.

Neurofilaments are well characterized in the ALS literature, and this is showing you some of the publications, with many of these in the last decade and with a particular focus in the last several years. Neurofilaments are increased in multiple neurologic diseases, some of which are shown here. While this increase in neurofilament is relatively nonspecific, ALS does stand out. Neurofilament levels are on the Y axis. If you look at neurofilament in red on the far left with serum neurofilament, or in the green box in the study on the right with CSF plasma neurofilament, you can see that it has clearly increased compared to multiple other neurodegenerative diseases; for example, 2 to 3 times higher levels than in Alzheimer's or Parkinson's.

This is another set of studies looking at

ALS compared to disease mimics, such as multifocal motor neuropathy. The Y-axis is CSF neurofilament light or heavy. In ALS, the neurofilament is increased and in other diseases, mimics are similar to control.

So how are we going to use neurofilaments in the ALS trials? There are three buckets to consider: identifying presymptomatic at-risk carriers for prevention trials, and this is used currently in the ATLAS trial, which I will discuss; also to control for disease heterogeneity in study populations, for example, ensuring treatment groups are balanced, and we've used that in the setting of the tofersen trial, as will be discussed by Dr. Fradette; and then assessing for lowering of neurofilament as evidence of a treatment effect.

If we are upstream and targeting the underlying pathophysiology of disease, and neurofilament is tightly linked with ALS, we would expect that neurofilament would be lowered and would be evidence of a treatment effect. Let me begin by discussing NfL as a susceptibility or risk

biomarker.

These are data from Michael Benatar looking at the time before symptom onset. These are asymptomatic gene carriers, measuring neurofilament in the serum on the Y-axis with time on the X-axis, plotted relative to the time of symptom onset. Each line is an individual gene carrier. Approximately 6 months before they show signs of disease, the gene carriers have an increase in the neurofilament, and this increase continues throughout their disease.

These early neurofilament changes have been incorporated into the ATLAS trial. ATLAS is a clinical study in asymptomatic SOD1 gene carriers. The goal of this study is to understand how early transition to tofersen can delay ALS symptoms. In part A, SOD1 gene carriers are followed clinically, and neurofilament is measured routinely. An increase in neurofilament moves a participant to the randomized placebo control arm, part B. This arm will test whether early treatment with tofersen will prevent the appearance of ALS signs and

symptoms. Clinical ALS moves the participant to the open-label tofersen.

We are controlling for disease heterogeneity in study populations, and I will show you a large amount of data and slides focused on this particular topic.

This is one set of studies showing that neurofilaments correlate with disease progression rate in the setting of ALS. On the Y-axis is the level of neurofilament. If you look at disease progression rate in the top left, you see a correlation. You can see if you break this down into slow, intermediate, and fast, on the top right, you see that the fast progressors are those, in general, that have a higher neurofilament level. The same thing is shown in the study below now with serum in the CSF NfL on the Y-axis, and ALSFRS slope, a measure of disease progression, on the X-axis. Higher neurofilament levels equal faster progression.

These are again separate studies showing that disease correlates with progression rate.

This is looking at disease progression rate on the X-axis and serum neurofilament light levels on the Y-axis; again, high neurofilament levels lead to a faster progression rate.

This is showing the same thing, but in a slightly different way. Here, let's compare the first quartile, the lowest level of neurofilaments, on the left, with the fourth quartile, the highest level of neurofilaments on the right. Look at the time on the X-axis, since this neurofilament was measured, and then look at the ALS Functional Rating Scale on the Y-axis.

Losing points in that scale would be evidence of doing worse. You can see that the first quartile, those with lower levels of neurofilament at, for example, 12-to-24 months, have lost some points, but in general, not that much. If you look at the fourth quartile, even at 6 months and at 12 months, they have lost many points on the ALS Functional Rating Scale, showing that they are progressing faster.

If you are progressing faster, you would

anticipate that the survival would be shorter, and that is what is shown in this next set of slides. The neurofilament levels are prognostic for survival. If you take a group of participants and divide them up above and below the median neurofilament level for that group, you can then look at survival probability on the Y-axis in each of the groups over time. You can see those with lower neurofilament levels, less than 116 in this particular example in green, with longer survival, and those in orange, greater than 116 in this example, shorter survival. So neurofilament is tied to survival.

This is another set of studies showing that neurofilament is prognostic for survival. It's the same sort of setup on the left with dividing the neurofilament levels into thirds, or groups, and looking at the percent survival on the Y-axis and the time on the X-axis. Those with the lowest neurofilament levels in green are surviving the longest.

What about neurofilament in the setting of

SOD1-related ALS? These are data from the VALOR study in the placebo participants. The Y-axis is the ALSFRS decline in the placebo group and the X-axis is the neurofilament level, and there was a relatively good correlation, 0.6, of the baseline plasma neurofilament with the progression rate. This would be consistent with the prior literature of singleton or sporadic ALS, showing that neurofilament is prognostic for progression and likely prognostic for survival in this population, too.

How about assessing for neurofilament as a treatment effect? There are not as many studies that have shown neurofilament and treatment effect. In fact, those are just beginning to emerge. I will show you a few examples here.

This is from the Spinraza study. Spinraza is an antisense oligonucleotide designed to increase levels of survival motor neuron protein, SMN. The loss of SMN1 gene is what causes spinal muscular atrophy, a childhood onset motor neuron disease. Spinraza changes the splicing of the

nearly identical sister gene, SMN2, that leads to normal full-length SMN protein, and thus had the ability to rescue spinal muscular atrophy.

In this study on the left is plasma neurofilament heavy. At about 9 weeks, you see that those treated with nusinersen in blue, compared to the sham control and the dashed black line, have a lowering of neurofilament. On the right, looking at survival, you see that there's a large effect of treating with nusinersen. That effect is somewhat delayed in terms of when we see the lowering of neurofilament. My interpretation of these data is that lowering of neurofilament predicts this future benefit of treating with nusinersen.

These are data from an ASO trial run by Biogen, treating participants with C9orf72-ALS. BIIB078 is an ASO designed to lower the levels of the sense strand of C9orf72. The mutation in C9orf72 is a large expansion of a hexanucleotide repeat within the gene. The expansion has an interesting biology in that hexanucleotide repeat

is in itself translated producing dipeptide protein GA and GP, for example. These dipeptides show up in the CSF.

In yellow are those treated with the antisense oligonucleotide compared to those in the blue dashed line. On the left, you see that the levels of the CSF polyGP and polyGA were reduced with treatment. This shows a clear effect of the antisense oligonucleotide doing exactly what it's meant to do, lowering the C9orf72 mRNA, and therefore lowering levels of these dipeptide proteins, which were presumed to be toxic.

If you then look at the effect on neurofilament in this study, which is shown on the top right in the same scheme, what you see is that those treated with the antisense oligonucleotide have an increase in neurofilament. One would say, "Oh, no. We've shown that increases in neurofilament is tied to faster progression rates, tied to worsening, which we would predict that this means that there's a greater breakdown of the axons in this study."

If you now look at the ALSFRS, these are relatively low numbers and some noise here and overlap. But if you look at those treated with placebo, they're in fact doing a bit better than those treated with the drug, and I've shown here this mild worsening that was seen across multiple different endpoints and measures. So this is showing, again, a correlation between function and neurofilament in this study. Based on these data, Biogen has decided to stop development of this molecule for C9orf72-ALS.

These are new data. These are not published. These are from my colleague, Dr. Bucelli, at Wash University, and he's been measuring neurofilament in a number of neuromuscular disorders. This shows you some examples of treatment response in neuropathies. All of the patients that I'm showing you had their clinical neurofilament measured, and they all did well with treatment. I'm showing you six examples of vasculitic neuropathies; POEMS; a checkpoint inhibitor neuropathy; and a sensory neuronopathy.

In each of these cases, neurofilament was lowered, and the patients improved, showing the treatment response part of neurofilament.

In summary, neurofilament can play, and has played, a critical role in ALS trials. When axons are injured or degenerating, neurofilament leaks into the CSF and blood. This appears to be particularly important for ALS in that the levels are high in the setting of ALS compared to many other neurodegenerative diseases. Neurofilament levels are prognostic for disease progression and survival. I showed you many studies coming to that exact same conclusion.

A lowering of neurofilament likely represents a slowing of axonal injury and neurodegeneration. In a study where we are treating the cause of the ALS, we would anticipate lowering neurofilament in that this would show us an effect on the disease. Given the clear link between neurofilament and disease progression and survival, this lowering that we see here provides evidence of a treatment effect.

I will now hand over to Dr. Fradette from Biogen to discuss tofersen efficacy. Thank you.

Applicant Presentation - Stephanie Fradette

DR. FRADETTE: Thank you, Dr. Miller.

Good morning. My name is Stephanie Fradette, and I am the clinical development lead for the tofersen program and the ALS portfolio head at Biogen. I'm quite grateful for the opportunity to speak with you today. Over the course of the next 30 minutes or so, I'll summarize the data informing the effectiveness of tofersen and supporting that neurofilament is a biomarker that is reasonably likely to predict clinical benefit in SOD1 ALS.

As Dr. Miller described, SOD1 ALS occurs because accumulation of toxic or pathological SOD1 protein leads to degeneration and death of motor neurons. Tofersen, as shown here in green, is designed to degrade SOD1 mRNA to reduce production of new SOD1 protein. By reducing accumulation of new toxic SOD1 protein in motor neurons and leveraging the body's natural clearing mechanism to

remove existing toxic protein, tofersen is expected to preserve motor neuron integrity to slow the neurodegenerative process.

In SOD1 ALS, we have the luxury of a reliable mouse model to assess efficacy preclinically. In G93A mutant mice, administration of tofersen before disease onset led to reductions in neurofilament, preservation of compound muscle action potential, maintenance of weight and motor performance, and prolonged survival.

With these preclinical data in hand, tofersen was moved into the clinic in a phase 1/2 single and multiple ascending dose study. The top dose of 100 milligrams, administered over 3 months and shown here in green, lowered SOD1 protein levels, providing indirect evidence of target engagement, and lowered neurofilament levels, suggesting a slowing of axonal injury and neurodegeneration.

We also saw exploratory clinical signals suggestive of a slowing of decline in clinical function. Those signals were primarily driven by a

small subset of very rapidly progressing participants in which the placebo group declined a great deal over the short study period. Data from these participants were foundational to the design of the phase 3 VALOR study.

VALOR was a phase 3, randomized, placebo-controlled study in adults for SOD1 ALS. The study was initiated in March of 2019 and enrolled 108 individuals globally over approximately 2 years. Building on what we saw in that phase 1 study, we assumed we could identify a subset of participants with rapidly progressive disease to comprise the primary analysis population or the faster progression subgroup. You may also hear us refer to this group as the modified intent-to-treat population. It has many names, but all are referring to the same group.

This population was defined according to SOD1 mutation type and pre-randomization ALSFRS-R slope, or the rate of decline on the ALS Functional Rating Scale from symptom onset to the study baseline, and we thought that in this primary

analysis population, the placebo participants would decline quickly, as we saw in that phase 1 study, enabling detection of a treatment effect over a relatively short 6-month study period.

To understand the effectiveness of tofersen across the broader SOD1 ALS population, we also enrolled individuals expected to progress more slowly. We'll refer to this group as the slower progression subgroup or the non-modified intent-to-treat population.

The primary endpoint for VALOR was the change from baseline to week 28 in the Revised ALS Functional Rating Scale total score, analyzed via the joint rank test in that primary analysis population. Secondary endpoints included changes in total SOD1 protein, again, as an indirect marker of target engagement; plasma neurofilament light as an indicator of axonal injury and neurodegeneration; percent predicted slow vital capacity as a measure of respiratory strength; hand-held dynamometry megascore as a measure of strength; and ventilation assistance-free survival

and overall survival.

Upon completion of VALOR, participants were offered the opportunity to enroll in the ongoing open-label extension study or the OLE. It's worth noting that participants, site staff, and the firewall study team for this extension remained blinded to individual treatment assignments from VALOR.

Anticipating that longer term follow-up would be important, the tofersen development program was prospectively designed to evaluate crossover to active tofersen by integrating data from these two studies. This integration enables comparison of early-start tofersen, or those who initiated to tofersen in VALOR, and delayed-start tofersen, those who had the opportunity to initiate 6 months later in the extension.

Integrated data from VALOR and the latest efficacy data cut of the extension, which occurred in January 2022, form the basis for evaluation of the effectiveness of tofersen. While VALOR was ongoing, our understanding -- the ALS field's

understanding -- of key aspects of clinical trial design was evolving. Prior to completion of VALOR or any analysis of the data, we appreciated that intra-mutation variability and non-linear decline on the ALS Functional Rating Scale could meaningfully reduce the prognostic strength of these measures, particularly over a short study period.

Fortunately, the ALS community had been working over the past decade, particularly over the last few years, to characterize the behavior of neurofilament in ALS. These studies have consistently found that neurofilament levels are prognostic for disease progression and survival. The higher the level of neurofilament, the more quickly progressing the disease.

On the left, we see one of many demonstrations of this shared by Dr. Miller. The graph shows that individuals with a neurofilament level above the population median in the study had shortened survival compared with those with the level below the median; and as Dr. Miller noted, we

have seen this relationship reproduced across the ALS literature.

In a study by Alexander Thompson, Martin Turner, and colleagues, published just last year, it was found that neurofilament levels in plasma were the only variable that independently predicted survival in people living with ALS. Other characteristics that we typically use to enrich, stratify, or confirm treatment groups are balanced, including the ALSFRS-R progression rate, as was used in the VALOR study, were not independent predictors of survival.

With increased confidence in the relevance of neurofilament levels, we also prespecified analyses in disease progression subgroups according to baseline plasma neurofilament light levels. Those with a baseline level above the median were considered faster progressors, and those below the median were considered slower progressors.

This slide summarizes the participant disposition from the start of VALOR for the January 2022 data cut. As shown at the top,

108 participants were randomized 2 to 1 in VALOR and comprised the full intent to treat, or ITT, population. Of those 108, 95 enrolled in the extension and 67 remained ongoing in the study as of that January data cut.

In green on the left, you'll see the participants originally randomized to tofersen who had the opportunity to continue tofersen in the extension, again referred to as the early-start group, and in blue on the right, you'll see participants randomized to placebo in VALOR who had the opportunity to cross over to receive tofersen in the extension approximately 6 months later, and again, we'll refer to this group as the delayed-start group.

Individuals carrying 42 unique SOD1 mutations were enrolled in VALOR. The two most common mutations included the I114T mutation, known to be fairly heterogeneous in nature, and the A5V mutation, typically associated with rapidly progressive disease. Many clinical characteristics of these participants at baseline were similar

between groups, including use of riluzole and edaravone; time from onset of symptoms; percent predicted SVC; and ALS Functional Rating Scale score.

That said, neurofilament concentrations were higher in participants who received tofersen than in those who received placebo at baseline. The tofersen group also had a faster rate of decline on the ALS Functional Rating Scale at study entry or the decline from screening to day 15, which is what one might expect, given the higher levels of neurofilament.

These imbalances were most pronounced in the disease progression subgroups defined by mutation and ALSFRS-R slope, including that primary analysis population. Though we can't say for certain these are clinically relevant differences, together they suggest that the participants randomized to tofersen were progressing more quickly at study start than those randomized to placebo. Importantly, in the disease progression subgroups, defined according to baseline neurofilament levels

instead of mutation and slope, these imbalances were minimized.

In VALOR, tofersen-driven reductions in CSF SOD1 protein were observable by about week 8, as shown on the left side of the slide. On the right, we see that tofersen-driven reductions in plasma neurofilament light were maximized by about week 16, where we see levels reach their new nadir before stabilizing.

Shown on this slide are the analyses in that primary analysis population or the faster progression subgroup, but tofersen-driven reductions in SOD1 protein and neurofilament were also observed in the slower progression subgroups. Despite the fact that tofersen seemed to achieve target engagement and slowed the neurodegenerative process, statistical significance was not achieved on the primary analysis in VALOR. Again, this is the change from baseline in the Revised ALS Functional Rating Scale over 28 weeks in that primary analysis population, and this is assessed via the joint rank test to account for mortality;

however, trends consistently favor tofersen across key secondary endpoints, shown here, as well as exploratory measures of quality of life.

As shown a moment ago, reductions in CSF SOD1 protein of approximately 30 to 40 percent and reductions in plasma neurofilament light of approximately 60 percent were observed in the tofersen group. Participants in the tofersen group also experienced a clinically relevant slowing of decline and slow vital capacity of 7.9 percent predicted relative to placebo. Though it favored tofersen, there was not much differentiation on HHD and the median time to death, and death or permanent ventilation were not reached in either group due to the limited number of events.

These differences favoring tofersen were particularly apparent in the faster progression subgroup defined by baseline neurofilament levels, as shown here. At 6 months, there was a 3.9 point difference favoring tofersen on the ALF Functional Rating Scale and a 9.9 percent predicted difference on SVC. The consistency of findings across

endpoints, coupled with the strong scientific plausibility associated with this target, this mechanism of action, suggested that the findings were not likely due to chance, and encouraged us to interrogate key aspects of the study design to better understand the primary results. This exercise shed light on several aspects of study design, which likely influenced the primary analysis in VALOR, core to which are the approach to controlling for disease heterogeneity and the 6-month study duration.

Data from VALOR reinforced the utility of neurofilament as a tool to control for that disease heterogeneity, which we know to be pervasive in ALS trials. As shown on the left side of this slide, data from the placebo participants in VALOR reaffirmed what the broader ALS literature tells us; that baseline plasma neurofilament levels are more strongly prognostic for disease progression over time at the ALSFRS-R progression rate. In hindsight, this observation further validates the decision to define alternative subgroups according

to baseline neurofilament levels, which, as discussed, corrected for key imbalances in baseline characteristics.

This categorical subgrouping above and below the median was a step in the right direction, but admittedly, the median is an arbitrary cutoff depending on the population enrolled. Instead, adjustments for baseline neurofilament as a covariate controls for individual heterogeneity with greater precision.

We had prespecified sensitivity analyses which did just that in the faster and slower progression subgroups for the original VALOR analyses, but those subgroups were still confounded by the use of mutation and ALSFRS-R slope upon which they were defined. With these learnings in mind, we amended the integrated efficacy analysis plan prior to analysis of the January 2022 data cut to include covariate adjustment for baseline levels of neurofilament in analyses of the full ITT population.

Now I'll spend a moment on study duration.

VALOR was designed with the intent to detect a clinically meaningful difference as quickly as possible, and based on the natural history data we had in hand at the time, we assumed this could be accomplished in a 6-month trial. That said, we overestimated the 6-month decline in the placebo arm by about 3-fold.

The sample size for the VALOR primary analysis population was calculated based on data from 12 placebo participants who matched the VALOR eligibility criteria from the phase 1 tofersen study, shown in black, and a study of arimoclomol, shown in gray. Based on these data, we assumed a 24.7 point decline in the ALS Functional Rating Scale over 28 weeks, so what we observed in VALOR was an 8.1 point decline, shown here in blue. Furthermore, a short relatively small study is susceptible to an imbalance of death due to chance, unrelated to the disease or therapy, and this can be particularly impactful when analyzing change in the ALSFRS-R via the joint rank test.

We observed only one death in VALOR, which

occurred in the tofersen arm, and this death was unrelated to ALS disease progression in study drug, according to the investigator. Importantly, we underestimated the time needed to achieve maximum biological activity with tofersen and the time needed for that biological activity to translate to clinical benefit. Taken together, these data suggest that a longer and larger study would have been required to appropriately account for the disease heterogeneity present in the SOD1 ALS population.

The prospective integration of VALOR in its extension gave us the opportunity to look beyond 6 months. Subsequent slides illustrate these integrated analyses from the January 2022 data cut, comparing early-start and delayed-start tofersen. These analyses follow the ITT principle, and thus include all 108 participants randomized in VALOR with adjustments for baseline neurofilament as a covariate.

At the time of randomization in VALOR, the treatment sequence for these integrated analyses

for whether a participant was in the early-start or delayed-start group was predetermined, and as noted, the study participants, site staff, and study management team remained blinded to VALOR treatment assignments in an effort to protect the integrity of ongoing data collection in the extension.

While these analyses are considered largely exploratory, effects consistently favor early-start tofersen across measures of strength, function, quality of life, and survival, despite the opportunity for the control arm to cross over to active treatment after 6 months. These data provide important clinical context regarding the relationship between tofersen-driven reductions in neurofilament and clinical benefit over time.

Here, the early-start group is shown in green and the delayed-start group in blue. The dotted portion of the blue line depicts the placebo period. Over 52 weeks, the delayed-start group declined by 3.5 points more than the early-start group on the Revised ALS Functional Rating Scale,

with a nominal p-value of 0.0272. Early-start participants, again shown in green, experienced less decline across all four domains of the scale: gross motor, fine motor, bulbar, and respiratory.

This forest plot illustrates the effect of early versus delayed-start tofersen on the ALS Functional Rating Scale when incorporating different approaches to controlling for disease heterogeneity. The top row depicts the analysis as showed on the previous slide in the full 108 participant ITT population, with adjustment for baseline plasma neurofilament light as a covariate.

Recognizing this specific analysis was incorporated in the integrated statistical analysis plan only after the original VALOR readout, we thought it was prudent to confirm the effect was directionally similar when analyzed in different subgroups using different covariate combinations. The first six rows illustrate the effect in the full ITT population when controlling for a different covariate combination. Below that are analyses in the disease progression subgroups,

defined according to a mutation and ALSFRS-R slope, and finally, the disease progression subgroups defined according to baseline neurofilament light levels.

This slide reinforces the relative strength of different approaches to controlling for disease heterogeneity and suggests reduced variability when we incorporated neurofilament as a covariate in the full ITT population. But regardless of the population or covariates adjusted for, all analyses consistently favor early-start tofersen.

Most deaths in ALS are associated with respiratory failure or its complications, and it is widely known that as vital capacity declines, the risk of death increases. Dr. Jinsy Andrews and co-authors found that slowing of the rate of decline in SVC 1.5 percent predicted per month reduced the risk of death after 6 months by 23 percent.

As shown here, the delayed-start group declined by 9.2 percent predicted more, over 52 weeks than the early-start group, with a nominal

p-value of 0.0159, a highly clinically relevant difference even with crossover in the control arm. It's also worth highlighting that in the delayed-start arm, we see an apparent stabilization in respiratory strength after week 40, which is the time point at which we'd expect maximum biological activity, around 16 weeks after initiation of tofersen.

Here again with SVC, we can quickly look at a variety of analyses using a forest plot. As with the ALSFRS-R, effects consistently favor early-start tofersen. The lowest p-value is associated with the analysis in the full ITT population, controlling for baseline neurofilament, which offers the most precise control for heterogeneity, but every variation on this analysis is directionally consistent.

Loss of muscle strength is a hallmark of ALS and a direct result of motor neuron loss. This slide illustrates the effect of tofersen on muscle strength as measured by hand-held dynamometry. To calculate the HHD megascore, individual strength

values from 16 muscle groups, 8 bilaterally, were normalized to Z scores and averaged. Participants in the delayed-start group declined by 0.28, more than the early-start group over 52 weeks, with a nominal p-value of 0.0188.

While this numerical value does not have explicit clinical meaningfulness, it is clearly in favor of early-start tofersen, suggesting a slowing of the loss of strength. In ALS, loss of strength is progressive, and improvements in strength are inconsistent with the natural history of the disease. This is evident in the dexpramipexole EMPOWER study, in which only 41 of 942, or 4.4 percent of participants, showed an improvement in strength over 52 weeks.

In the delayed-start tofersen group, this proportion was nearly doubled, with 8 percent of participants experiencing increases in strength over the same period of time. In the early-start group, 27 percent of participants experienced an increase in strength over 52 weeks, and once again, we can look at a forest plot for HHD. As with the

ALSFRS-R and SVC, we see consistent effects favoring early-start tofersen, regardless of the approach to defining the population and regardless of which covariates are used.

Just as critical to the understanding of treatment effect is traditional clinical outcome measures or patient-reported quality-of-life measures. The ALS Assessment Questionnaire-5, or the ALSAQ-5, is an ALS-specific, patient-reported outcome measure designed to assess one's ability to stand up, use arms and hands, eat solid food, speak clearly, and feel hopeful about the future. The scale runs from 0 to 100 with higher scores depictive of worsening.

The early-start group maintained greater quality of life with a 10.3 point difference between groups. The EQ-5D-5L is a 5-dimension questionnaire to assess decline in health status across various conditions. The questionnaire assesses dimensions of physical mobility, self-care, usual activities, pain and discomfort, and anxiety and depression. Here we saw a large

difference of 0.2, favoring early-start tofersen. And finally, the Fatigue Severity Scale, which assesses domains including life participation, sleep, and daily activities, is the one instance where a clear differentiation between treatment group was not observed, though the results still favored early-start tofersen.

Weight loss is known to be a strong independent predictor of survival in ALS. In VALOR, the mean weight decreased by 1.6 kilograms, or 3.5 pounds, in the placebo group, and increased by 0.5 kilograms, or 1.1 pounds in the tofersen group, painting a consistent picture as is seen with other clinical measures.

Now we'll turn to time-to-event analyses for early versus delayed-start tofersen, which incorporate all available follow-up as of the January 2022 data cut. This figure depicts the Kaplan-Meier curve for time to death or permanent ventilation. Permanent ventilation was defined as at least 22 hours of ventilatory support for at least 21 consecutive days. As of the January data

cut, all participants enrolled in VALOR had the opportunity for at least 1 year of follow-up with a median of 2.3 years. Despite this duration of follow-up, neither treatment group reached the median due to the limited number of death-equivalent events.

Shown here are the proportion of relevant events in the early- and delayed-start groups and the associated hazard ratios. We interpret these results of caution due to the limited number of events, but the hazard ratios are noteworthy. To briefly summarize, early-start tofersen was associated with a 64 percent reduction in the risk of death or permanent ventilation, and a 73 percent reduction in the risk of death as compared to delayed-start tofersen. Similarly, low hazard ratios are observed when incorporating post-withdrawal vital status data and when also considering withdrawal due to disease progression, as assessed by the investigator, a death-equivalent event.

While the median was not reached in either

treatment group for the full ITT population, we can also evaluate time-to-event analyses in neurofilament-based subgroups. Shown on the left is the Kaplan-Meier curve for the below the median neurofilament light group, where you see a very limited number of events, consistent with the slower progressing nature of the disease. Importantly, no events of death or permanent ventilation have been observed in the early-start group as of that January data cut.

On the right is the curve for the above-the-median neurofilament group, which, as would be expected, experienced a larger number of events. Here we can calculate a median time to death or permanent ventilation in the delayed-start group of 1.5 years. Although the median for the early-start group has not been reached as of the data cutoff, this represents at least a 1-year extension in event-free survival.

We are also able to calculate a median follow-up time in the subgroup of A5V carriers enrolled in VALOR using observed data. The median

follow-up time represents the median time from symptom onset to death, withdrawal due to disease progression, or the last contact in the study as of that January data cut. The yellow arrows indicate the individuals still participating in the extension.

This is an important analysis because the A5V mutation is among the best characterized as SOD1 mutations, with a median survival of 1.2 years or less. In the 11 A5V carriers in the early-start group, the median follow-up time from symptom onset was 1.9 years. This is nearly 50 percent longer than the 1.3-year median observed in the delayed-start group.

The consistency and timing of the biological and clinical effects support that tofersen is having a disease-modifying effect. It took about 8 weeks to achieve maximum reductions in SOD1 protein, consistent with the pharmacokinetics of tofersen and the estimated half-life of SOD1 protein. Around 16 weeks after tofersen was initiated, neurofilament levels reached their new

nadir; again, something that one might predict would occur only when SOD1 levels have been sufficiently reduced.

At 28 weeks, trends suggested tofersen was slowing decline on clinical outcome, but these effects were not statistically significant. By 52 weeks and beyond, there is consistent evidence that earlier initiation of tofersen is reducing decline in strength, function, and quality of life, and in some cases leading to improvement. The data also indicate that earlier initiation of tofersen is reducing the risk of death-equivalent events, which we will continue to follow over time in the ongoing extension study.

I'll take a moment to expand on why this sequence of events has such strong biological plausibility. The first step is stopping or slowing the upstream cause of the neurodegeneration; in this case, production of toxic SOD1 protein. This then allows degenerating motor neurons to stabilize, as evidenced by reductions in neurofilament.

Those neurons that are no longer contributing to force generation need to re-establish neuromuscular transmission with their original myofibers, and if they've recovered sufficiently, they can sprout collaterals to other denervated myofibers; then neuromuscular junctions have to mature, become more efficient, before the reinnervated myofibers can begin adding myofibrils, eventually contributing additional force to muscle contraction. Only after all of that has occurred will it manifest as improved strength, as measured by dynamometry or vital capacity, for improved motor function, as measured by the ALS Functional Rating Scale.

With these data in mind, we'll now turn to discuss why tofersen-driven reductions in neurofilament are reasonably likely to predict this clinical benefit.

Dr. Miller reviewed the ALS literature supporting the use of neurofilament as a susceptibility or risk biomarker and a prognostic biomarker of disease progression and survival.

I'll now focus on the information supporting use of neurofilament as a biomarker of treatment response and a surrogate biomarker reasonably likely to predict clinical benefit in SOD1 ALS.

To very briefly recap, robust lowering of neurofilament has been seen with tofersen administration, both preclinically and clinically, suggesting that lowering of toxic SOD1 protein is reducing axonal injury and neurodegeneration. These reductions are observed in people with different SOD1 mutation types, rates of disease progression, and stages of disease, and appear to be sustained over time.

As shown on this slide, the effects of tofersen on neurofilament are similar across isoforms and matrices; that is tofersen led to reductions in neurofilament light and phosphorylated neurofilament heavy, and these reductions were observed in both plasma and CSF. As we presented today, these reductions in neurofilament were fully apparent within about 16 weeks of tofersen initiation, prior to

discernible evidence of clinical benefit.

We observed reductions in neurofilament in nearly all tofersen-treated participants in VALOR. A natural follow-up question is whether we see the greatest clinical benefit in those participants with the greatest lowering of neurofilament, but this individual comparison can't be made without accounting for the expected natural disease progression in each individual.

Let's use participants A and B noted here as an example. Participant B had a baseline neurofilament light level of 211, suggesting a disease progression more rapid than that of participant A, who had a baseline level of 62. So both had a similar percent reduction in neurofilament, and one would not expect the impact on clinical outcome measures to also be similar because they were destined to have different declines if left untreated.

Any comparison of the clinical impact of tofersen in these two participants would have to take these differences in disease trajectory into

account. In aggregate analyses, this can be done by adjusting for baseline neurofilament as a covariate. To understand the clinical relevance of neurofilament reductions on an individual basis, we developed the statistical model, which I'll introduce on the next slide.

This model was developed with a causal inference component to characterize the relationship between early tofersen-driven reductions of plasma neurofilament light and slowing of clinical disease progression over time. The model accounts for differing rates of natural disease progression across participants, recognizing that those with higher baseline neurofilament levels are expected to decline more quickly or experience shorter survival than those with lower baseline levels.

The concept underlying the model is illustrated on the left side of the slide. It essentially deconstructs the observed treatment effect for a tofersen-treated participant into three components: first, the change due to the

expected natural disease progression, which is estimated using data from the VALOR placebo or delayed-start participant; second the change due to the tofersen effect through the neurofilament light pathway, which is particularly relevant in the case of tofersen, given its mechanism of action; and finally, the change due to the tofersen effect through non-biomarker pathways or factors. This last category is a bit more abstract, but examples would be effects attributable to an adverse event or effects of the therapy unrelated to slowing of neurodegeneration. As one would expect, this component was not found to be significant for tofersen.

The model takes the baseline neurofilament light level in a tofersen-treated participant to estimate what their neurofilament would have been at week 16 without tofersen. It then uses those values to predict what would have occurred without tofersen at week 28 for measures of strength, function, quality of life, and over time for measures of survival. This then can be used to

compare the observed trajectory and the predicted trajectory without treatment, and estimate the magnitude of slowing and disease progression or the reduction in risk associated with tofersen-driven reductions and plasma neurofilament light.

The model demonstrates a relationship between early tofersen-driven lowering of neurofilament and reductions in worsening on the ALSFRS-R, SVC, HHD, ALSAQ-5, and the EQ-5D-5L over time. As an example, let's look at the relationship for an individual with a baseline plasma neurofilament light level right around the VALOR sample mean for approximately 97 picograms per mL. The table on the right shows us that for each 10 picogram per mL reduction in plasma neurofilament light levels at week 16, when we reach the nadir, you'd expect a reduction in worsening on the ALSFRS-R of 0.772, that differently, a 50 percent reduction in neurofilament, which would be associated with a 2.47 point reduction in the worsening on ALSFRS-R week 28.

This relationship is dynamic such that the difference would be greater in an individual with a higher baseline neurofilament level and faster disease progression, where there would be a greater opportunity to differentiate from natural disease progression.

In the model data, the delayed-start participants were used to conservatively estimate the event risk driven by natural disease progression. While the number of events is limited, reductions in neurofilament at week 16 were, again, associated with a reduction in event risk. For that same participant with a baseline plasma neurofilament light level of approximately 97 picograms per mL, a 10 picogram per mL reduction in plasma neurofilament light at week 16 is associated with a reduction in event risk, ranging from 16.1 to 24.9 percent across the four survival endpoints listed here.

To date, there have not been data sets to pull from to replicate the model with data from other therapies due to the absence of neurofilament

lowering, but that may be changing soon, as more and more researchers are incorporating neurofilament as a key component of their ALS clinical trials. Importantly, the results of the model reflect what would be expected with a therapy targeting the underlying pathophysiology of SOD1 ALS, and are consistent with observations in VALOR, and its extension more broadly.

In summary, we know that SOD1 ALS is a disease in which toxic SOD1 protein leads to motor neuron degeneration and death. We know that as those motor neurons are degenerating, they're leaking their neurofilament, which is passing into the blood and CSF. Consistently, we know that higher levels of neurofilament are associated with faster disease progression and shortened survival and ALS.

There are certainly reasons why one may not observe a lowering of neurofilament with an effective therapy in and ALS. For example, while possible that a therapy focused on muscle or neuromuscular junction could benefit the motor

neuron and stabilize axon, it would be much less likely, and yet these types of therapies could provide benefit. But there appears to be consensus within the ALS community that a lowering of neurofilament represents a slowing of axonal injury and neurodegeneration and provides important evidence of a positive treatment effect.

As tofersen is designed to reduce production of SOD1 protein, it is expected to preserve motor neuron integrity, and thus reduce levels of neurofilament, and that is what we see. As demonstrated with the VALOR and extension data and the statistical model presented to date, these reductions proceeded and predicted slowing of decline in strength, function, and quality of life, and a reduced risk of death-equivalent events. In summary, there is strong biological plausibility and empirical evidence supporting that reductions in neurofilament are reasonably likely to predict clinical benefit in SOD1 ALS.

In the context of a potential accelerated approval, Biogen has proposed a confirmatory

evidence generation plan, which accounts for the rarity of SOD1 ALS and prioritizes speed to availability of data. Confirmation of clinical benefit could come from data generated from the currently enrolling ATLAS study, an ongoing adequate and well-controlled trial that is designed to evaluate the effects of tofersen when initiated in clinically asymptomatic SOD1 mutation carriers with biomarker evidence of disease activity or elevated plasma neurofilament light levels.

ATLAS will evaluate whether tofersen can halt or delay the onset of clinically manifest ALS. The study was initiated in 2021, and we've enrolled 84 of 150 participants or over 50 percent of the target population to date. Based on the current study design and enrollment rates, data are expected from the ATLAS trial as early as 2027. These data will be further supported by combined analyses of data from VALOR and final data from the extension study, expected to conclude in 2024; variant-specific survival analyses incorporating data from tofersen trials; the global expanded

access program; and disease registries and available natural history data sets.

Ultimately, the agency will determine what constitutes an adequate confirmatory study, but should tofersen receive accelerated approval, Biogen is committed to confirming the clinical benefit of tofersen in SOD1 ALS as quickly as possible. And with that, I will hand it over to Dr. Laura Fanning to review the safety profile of tofersen.

Applicant Presentation - Laura Fanning

DR. FANNING: Good morning. My name is Laura Fanning. I'm an allergy/immunology specialist and a drug safety physician, and I lead medical safety for neuromuscular and movement disorders at Biogen. Today I'll be describing the safety profile of tofersen.

The integrated safety analysis for tofersen focused on two main populations, the pivotal study VALOR, which allows direct comparison of tofersen with placebo and the pool of people SOD1 ALS who received 100 milligrams of tofersen at any time in

the clinical studies, which I will refer to as the integrated population.

This integrated population falls into a few different categories. These could be participants who started out in earlier parts of the placebo-controlled Study 101, parts A or B, which were the single and multiple ascending dose parts of the study. They could also be participants in the VALOR study who received tofersen 100 milligrams from the outset, or participants from the placebo portion of the VALOR study who later moved into the open-label extension and received 100 milligrams of tofersen there. The total size of this integrated population is 147 participants.

With regard to the overall extent of tofersen exposure, the VALOR study, which was 6 months in duration, had a median exposure of 28.1 weeks. The integrated population -- again, 147 participants -- had a median of 119 weeks or approximately 2 years of exposure to tofersen 100 milligrams. Multiple participants have been on

tofersen for greater than 3 years, and the maximum duration of exposure is 212 weeks or about 4 years.

Before going through the safety overview, I'll first note that the tables on this slide and subsequent slides are similar in format, so I'll take just a moment to orient everyone to the format of the slides. On the left side in the first two columns we're showing the VALOR study with the tofersen group, 72 participants in the first column, and the placebo group, 36 participants in the second column. The right side of the slide shows the integrated 100-milligram population of 147 participants from Study 101 and the open-label extension study.

As you can see at the top of this overview table, nearly all participants had at least one adverse event, and looking to the second row, I'll note that most participants had at least one adverse event related to the lumbar puncture procedure, and this was similar, as you can see in the first two columns, between the tofersen and placebo groups.

Most adverse events were mild or moderate in severity, and in the third row you can see that 17 percent of participants in the tofersen group in VALOR had grade 3 or greater adverse events, which are severe, life-threatening, or fatal events. In the placebo group, 11 percent of participants had grade 3 or greater events.

Moving to the last two rows of this table, we can see that in the integrated population, 18 percent of participants had an adverse event leading to drug discontinuation, and many of these were also events with fatal outcome. I'll go into more detail on serious adverse events and adverse events with fatal outcome on subsequent slides.

Here in graphical format we're showing the most common adverse events reported in VALOR and the open-label extension. The green bars show tofersen 100 milligrams and the blue show the placebo group from VALOR. The orange color on the right side of each grouping shows the integrated population that received tofersen 100 milligrams at any time. Some of the most common adverse events,

such as headache and procedural pain, are events commonly associated with the lumbar puncture procedure.

Adverse events of increased protein or increased white blood cell count in the cerebrospinal fluid were also reported. I'll discuss some of these specific events further in the coming slides. I'll also note that most of the common adverse events are generally similar between the VALOR study experience and the integrated tofersen experience over time. Some events are more common in the integrated population due to the longer duration of exposure and the clinical trials for those participants.

As I mentioned, CSF lab abnormalities were reported as adverse events in a subset of participants in the tofersen clinical studies. Routine CSF labs were tested at the time of each intrathecal dose of tofersen or placebo in the clinical studies. Abnormalities in these labs were very common, and many were not reported as adverse events. Whether a lab abnormality is determined to

be an adverse event or not is up to the judgment of the investigator.

As you can see in this table, a majority of participants who received tofersen had at least one CSF white blood cell count greater than 10, and nearly all participants had at least one count greater than 5, which is the upper limit of normal range in many labs. Abnormalities occurred in the placebo group as well, but were more common in the tofersen group in VALOR. CSF protein data is a little bit more complicated because many people with ALS have abnormal CSF protein levels at baseline, but nearly all participants who had a normal protein level at baseline developed an elevated level at some point after receiving tofersen.

To dig more deeply into the lumbar puncture-related events, I'll first point out that the assessment of relatedness to lumbar puncture, referred to in this instance as the investigator assessment, as I mentioned earlier, most of the participants had at least one lumbar

puncture-related adverse event, and this was similar between the tofersen and placebo groups in the VALOR study. As you can see here, procedural pain, headache, post lumbar puncture syndrome, and back pain were the most common of these events, and that remained true both in the VALOR study and in the integrated population.

Serious adverse events were reported in about 18 percent of tofersen participants and 14 percent of placebo participants in VALOR, and in about 40 percent of the participants in the integrated tofersen population. The most common of these events included respiratory failure, aspiration pneumonia, and other events that are common in the ALS population as a whole.

With regard to adverse events with fatal outcome, there was one such event in the VALOR study in the tofersen group, which was congestive cardiac failure. In the integrated population, 19 participants, or about 13 percent, had an adverse event with fatal outcome and, again, the majority of these events were respiratory failure,

which is consistent with ALS disease progression and with the most common cause of death in ALS. None of these 19 fatal adverse events were assessed by the investigators as related to tofersen.

Serious neurologic events have been reported with tofersen and similar events have not been seen in the placebo group from the VALOR study, as you can see on this slide. These events can be grouped into three main categories. The first category consisted of events characterized by elevated intracranial pressure and papilledema.

The next category includes events with terms consistent with myelitis or radiculitis, and these occurred in the integrated population in a total of 6 participants. The third grouping consists of meningitis, which was reported with terms of aseptic or chemical meningitis, and in all of these categories, a few things have been consistent. In the majority of these events, participants were able to remain on study treatment, and in the few cases where discontinuation was necessary, the event did resolve completely. Evaluation and

management of all these events, regardless of the type of event, has consisted of measures consistent with the standard of care. For example, elevated intracranial pressure has been managed with diuretics such as acetazolamide.

In summary, tofersen was generally well tolerated in this SOD1 ALS population with an acceptable safety profile, and longer duration of exposure up to 3 years or more was not associated with new safety concerns developing over time. Adverse events, including lumbar puncture-related events, were generally mild to moderate in severity and not treatment limiting. There were serious neurologic events, including myelitis and radiculitis, papilledema, and aseptic meningitis reported with tofersen, and these were manageable with standard of care.

I'll now hand the presentation back to Dr. Miller to provide additional clinical perspective.

Applicant Presentation - Timothy Miller

DR. MILLER: Thank you, Dr. Fanning.

I am Tim Miller, neurologist/neuroscientist at Washington University in St. Louis, and I've been working on this therapy for SOD1 ALS for the last 20 years. I am delighted to be able to give you my clinical perspective on tofersen. I'm going to start by commenting on a few pieces of data from the study, and then share some of the details about individual cases.

This is looking at hand-held dynamometry or muscle strength. This is my favorite set of data from this publication, showing that those on early-start tofersen are seeing a clinical benefit. If you look from week 28 out to week 52, they're increasing in muscle strength. We looked again at these data and asked how many people had improvements from the baseline visit to the end of the study, week 52, and for early-start tofersen, an impressive 27 percent of them had an increase in muscle strength. Again, this was a really impressive change in the muscle strength.

While there are some noteworthy reports of a few isolated cases of ALS where there are

improvements, in my two decades of treating people with ALS, I have yet to see. It is strikingly uncommon. As Dr. Fradette reviewed, the EMPOWER study was a large ALS trial of dexpramipexole. This study of more than 900 participants included measurements of muscle strength, and looking at that study, only 4 percent showed improvement compared with baseline. While clearly not everyone improved, the fact that a quarter showed evidence of improvement after treatment with SOD1 ASO is truly remarkable.

This is another really striking piece of data from the VALOR study. The dashed blue line showing placebo group is what we typically see in people living with ALS; as the muscles atrophy, weight drops. In green is the tofersen-treated group. Their weight is stable to slightly increased. This is another piece of data reinforcing that the neurodegenerative disease process has been greatly slowed.

Those on early-start tofersen had fewer events of death or permanent ventilation. If you

look at the hazard ratio, there's a hazard ratio of 0.36 for those on early start compared to the delayed-start tofersen, so a reduction in the number of deaths and permanent ventilation. If we now look at the SOD1 A5V carriers -- this represents about 50 percent of the SOD1 mutations in the United States -- they are well known to be a rapidly progressive subgroup of ALS, and these are a number of studies looking at the survival of these populations. The mean disease duration, typically 1.2 years.

When we look at how this group, A5V, do in this study, the first point to highlight is that there are three ongoing participants, as shown with the orange arrows. The green is showing you when each of these participants received tofersen and blue is the placebo, and then the time since ALS symptom onset. You can see that the early-start tofersen survived 1.9 years and the delayed start, 1.3. For the early-start tofersen that is a 50 percent increase in the median survival compared to what the published data are in terms of survival

or compared to the delayed start.

There are serious neurologic events. There are events associated with lumbar punctures many would expect, and that is not shown here. What I'm showing you here are some of the serious neurologic events that occurred on tofersen and not on placebo. These were reviewed by Dr. Fanning and are things that we will need to continue to keep an eye on and to manage.

In summing it up, tofersen lowers the CSF SOD1 levels at about 8 weeks, and then tofersen reduces plasma neurofilament at about 12-to-16 weeks. This reduction in neurofilament, in my view, is evidence of a substantial slowing of the neurodegenerative disease process. At 28 weeks, we see some trends of slowing of decline, but it does take time to heal. At 52 weeks is when you really begin to see the data showing the benefits of tofersen: stabilization of clinical function, respiratory function, increases in strength, and improvements in quality of life, and also earlier initiation of tofersen showing a

reduced hazard of death or permanent ventilation.

I wanted to review some of the cases that I've been involved with in St. Louis and talk about some of these individual stories. There are four cases I'm going to go through. One is a participant that really has no worsening at all over several years. The other's a participant that declined during the study, but when the open-label extension started, they had some stabilization and then improvement.

Then I want to talk about the expanded access participants with reductions in neurofilament and stabilization of function. I do want to give a special thanks to Wash U colleagues, Bob Bucelli; Sean Smith; Amber Malcolm; Kelly McCoy Gross; Jesse Markway, for both generating these data and sharing these data for the discussion today.

This participant entered the trial in 2017. He was mildly symptomatic, mainly with falls. He rolled into the open-label extension and has been receiving 100 milligrams of tofersen for about

4 years. He has a long history of SOD1 ALS in the family, with many family members that have been affected that typically survived 5 to 10 years. This case illustrates the stabilization of function in the relatively slow progressing forms of SOD1 ALS.

His status in 2023, after being in the study for more than 5 years, he has fewer falls, increased function, and increased strength. He had an EMG in 2017 before he entered the study, and then again in late 2022. The changes on EMG in 2017 were mild, but if we look at them compared to 2022, his arms, 3 of 3 muscles tested in 2022 showed improvement compared with 2017. In his legs, one muscle that was normal in 2017 remained normal. One muscle showed mild improvement but still clearly abnormal, and one muscle with improvement.

The CMAP is the compound muscle action potential, the summation of all the electrical activity in the muscle and maximum stimulation of the motor nerve. Overall, consistent with his lack

of progression, his CMAPs are stable. Shown on the top right are his right arm and leg, and on the bottom, his left arm and leg. For an SOD1 family, where progression from onset to death is typically 5 to 10 years, the fact that he has stayed the same for the past 5 years is striking. He has told our group, "I don't feel like I even have ALS."

These are data from participants that have not been presented yet. These are from the long-term follow-up from the phase 1 study not part of the VALOR study, and in this analysis, looking at 40 participants, SOD1 ALS, that received at least one dose of 100 milligrams of tofersen. For many of these participants, there are now years of follow-up in the open-label extension.

So how much stabilization do we see in this group? First, there are clearly participants who declined, about 6 to 7, and you can see those lines going down, but there are many lines here, more than 30, that are nearly flat, absolutely stable over the course of the study, or perhaps improving a bit in the ALSFRS or in terms of their strength,

the HHD megascore. This was observed in many different participants, not just the one that I highlighted.

This was a participant in the phase 3 study. He entered it late 2020. He had a baseline plasma NfL of 63, and he was really not doing well at the time that he entered in terms of rapid disease course. He continued to progress rapidly in the study, and this case demonstrates one of the impressive stories of recovery of function.

This is showing you the breathing, ALS Functional Rating Scale, and strength in this participant, and you can see the study, and then the vertical bar is the open-label extension. He declined rapidly in the course of the study, and while we remain blinded, we have assumed he was on placebo. When I asked him how things were in the middle, he said he could not use his right arm hardly at all. He could not raise it above his head or do anything with it. He then recovered function, and you can see that in each of these measures.

I asked him how he's doing now, and he said, he can use his right arm to raise it above his head easily. He can pour from a gallon of distilled water and use his muscles. When I examined him myself, his arms were nearly full strength. He said he feels better. His speech was really different. He's no longer pausing to take breaths in between his words. He's speaking easily and comfortably. He's now in rehab with a physical therapist to try to relearn how to walk as his legs get stronger.

This recovery and function also correlates as a recovery in the compound muscle action potential. This is a summation of the electrical activity in the muscle when maximally stimulating the motor nerve, and you can see that he did have a decline in nearly all the area, and then began to have an increase in his compound muscle action potential, showing a physiologic correlate of the increases in strength that he has experienced.

I should note that any increase in CMAP in ALS is wholly unexpected. We would predict a slow

decline in the CMAP. One measurement would make us worry about noise, but the consistent values over many months with a slow rise to current increase in strength to me says that these are real increases and also really impressive.

Many clinicians listening to this will be familiar with the 1-to-5 grading scale of muscle strength. The scale was developed by colleagues at the Medical Research Council in the United Kingdom. The MRC scale is a 1 to 5, so 1, muscle movement with no limb movements; 2, movement in the plane or gravity; 3, movement against gravity -- and all of these are, therefore, super weak -- 4, is some strength; 5 is full.

If you look at these measurements at month 4 in the open label in dark blue, and then month 22 in the open label in the light blue, you can see substantial improvements on this clinical scale, and I hope that this gives many of the clinicians a quick impression of the magnitude of this gentleman's improvement.

How might there be a recovery in CMAP? We

do not have direct evidence in this study, but if we draw on recovery after traumatic injuries -- radiculopathy, polio, and other nerve injuries -- it is likely that we are enabling sick but not dead motor neurons to reinnervate or allowing sick neurons to become healthy and to connect to muscle.

Shown here in schematic form are two normal motor neurons connected to muscle with the compound muscle action potential shown below. Axonal degeneration leads to disconnect of the motor neurons in the muscle, and the CMAP decreases, and neurofilament leaks out. But with treatment, and healing, and time, the other motor neuron is able to reconnect all the muscle cells and the maximal electrical activity, and after stimulating the motor nerve, the CMAP then increases.

This is the first of the expanded access participants. Each of these expanded access demonstrates some early real-world experience, including a clinical lab measurement of serum NfL. This participant was able to walk, had some falls,

had difficulty with some tasks using his arms, but overall he was doing okay when he entered the expanded access.

The first thing to point out here is his serum NfL. His serum NfL declined by about week 16. This matches the published data from the clinical trial. I'll note that the serum NfL, as measured here, was measured in a clinical lab, not measured as part of the study, and not measured with colleagues at Biogen. His strength initially declined during the study but has begun to pick back up, in particular, in his arms. He's had improvement in strength, fewer falls that he reports, and with his arms, he is able to push off more easily to get out of a chair, which he was not able to do previously.

This is another participant in the expanded access. This was a young gentleman who had a relatively new diagnosis of ALS, but also in his family, and caused an SOD1 mutation that was known to be rapidly progressive. He had a precipitous decline in his NfL. Our interpretation of this is

a slowing down of the neurodegenerative disease process. He had an increase in his muscle strength as seen in the graph on the right. He has had an improvement in strength and also an improvement in function, which is what I will show in the next slide.

These are the three measures done by physical therapy. The Berg Balance Test, the Timed Up and Go using a rollator, and the 10-meter Walk Test. We think that this shows objective measures of his improvement over the course of the study. From other literature focused on functional recovery, the generally agreed-upon clinically meaningful change for Time Up and Go is about 2.1 seconds. He is double that.

For the 10-Meter Walk Test, clinically meaningful change is about 0.15 seconds, and he is triple that number. To people living with ALS and everyone involved in their care, these sorts of objective measures of improvement are unexpected, and I think wowing.

For those of you who know me and have seen

my presentations, you will know that I'm cautious to overinterpret. I've been reluctant to share too many of these stories for fear that my enthusiasm about these remarkable changes will be seen as over-the-top bias since I've been working on this for so long. So I'm coming back here to the published study to highlight that, as a group, at the later time points, those on tofersen for 52 weeks showed evidence of increases in strength.

The examples that I just showed you give some color to these types of data, but there are now many examples of similar stories. And while I'm convinced that Dr. Bucelli and Washington University neuromuscular colleagues are among the best in the world, and thus might be able to uniquely help some ALS patients, our experience is, in fact, not unique.

The effect of this drug on clinical function has been recognized by many groups around the world, from a consensus statement from our European colleagues, the consensus view of TRICALS neurologists, is that tofersen shows clear benefit

for people with ALS due to SOD1 mutation, especially if given early in the disease course, and support should be given for licensing in this group of patients.

From Merit Cudkowicz, director of the Healey Center at MGH and leading ALS clinical trialist, "In my 30 years as an ALS physician, this is the first study where I have personally seen people stop progressing, and some of them recover function. The dramatic effect also on NfL is a huge step forward for the field."

From Pam Shaw, "First time participating patients have reported an improvement in their motor function." From the participant, "I can walk without my poles. I can climb my garden steps, which I haven't been able to do for two years. I can write my Christmas cards this year, which I couldn't do last year." These are some really poignant examples of increases in function and that other people have clearly recognized among those who have been treated with tofersen.

These medications represent an important

advance for the osteo, but none of them bends the curve enough for participants and patients to feel the difference in terms of disease progression. The published data and the anecdotal stories, some which I shared with you, suggest that tofersen has a major impact on disease progression and is clearly a game-changer.

So putting it all together, SOD1 ALS is a serious, progressive, ultimately fatal disease with significant unmet medical need. Adverse events warrant consideration, in particular serious neurologic events, but in the context of the severity of the disease and the effects demonstrated, the potential benefits outweigh the potential risks. A reduction in neurofilament indicates a slowing of the neurodegenerative disease process. Tofersen has demonstrated clear potential for stabilization or improvement of clinical function, strength, and quality of life.

Case reports and individual stories of improved strength and function are consistent, and remarkable, and unprecedented. These stories would

not be possible without the efforts from many funding agencies, individual scientists, principal investigators, super hardworking site staff, and in particular, the brave volunteers who participated in these studies and their caregivers. They are deeply appreciated. I also want to thank those who submitted the 146 comments, many of which are heartfelt, personal, and validating. I also want to thank in advance those participating in the open public hearing this afternoon.

As a clinician treating ALS and seeing firsthand both the incredible hardships created by ALS and also some of these striking recoveries, there is an urgent need to make tofersen available as soon as possible. Now I'd like to re-invite Dr. Stephanie Fradette for our closing presentation.

Stephanie?

Applicant Presentation - Stephanie Fradette

DR. FRADETTE: Thank you, Dr. Miller, and keeping an eye on time, Dr. Montine, so we'll make this quick. This is Stephanie Fradette from Biogen

again.

VALOR was designed five years ago with the intent to demonstrate clinical benefit on the ALS Functional Rating Scale over 6 months. We acknowledge that this objective wasn't achieved and that the integrated VALOR and extension clinical analyses are considered largely exploratory. Although plasma neurofilament light was prespecified as a secondary endpoint, this was done without the foresight that it would form this primary basis of an NDA submission for accelerated approval.

The field has evolved greatly over the past several years, both its understanding of ALS trial design and its understanding of the relevance and behavior of neurofilament in ALS, particularly over the last few years. We've adapted to this evolving understanding in real time to perform the most robust and objective analysis of the data in hand, and this has led us to this advisory committee meeting today.

SOD1 ALS is a relentlessly progressive and

uniformly fatal disease, as you've heard today, and for the estimated 330 people in the U.S. currently living with the disease, there is an urgent unmet medical need. This is a disease in which toxic SOD1 protein leads to motor neuron degeneration and death, and as those motor neurons are degenerating, they're releasing neurofilament.

Tofersen is designed to address the root cause of SOD1 ALS by reducing production and accumulation of this toxic protein to slow the degeneration of motor neurons, as evidenced by the reductions in neurofilament. These neurofilament reductions proceeded and predicted slowing and decline in strength, function, and quality of life, and a reduced risk of death-equivalent events. There is substantial evidence tofersen reduces neurofilament and that this reduction is reasonably likely to predict clinical benefit for people living with SOD1 ALS.

Recognizing the limitations of the analyses discussed today, consistent biological and clinical benefits of this magnitude, including some evidence

of clinical improvement, have not been seen in ALS trials to date and are completely inconsistent with the natural history of the disease. The consistency across measures and the temporal relationship of the effects observed suggests that the probability that these observations are due to chance is very low.

The serious neurological events discussed today warrant awareness and consideration, but in the context of the severity of the disease and the observed treatment benefits, the overall benefit-risk is considered favorable. We acknowledge the committee is being asked for input on both accelerated and traditional approval pathways. In either scenario, Biogen is committed to continuing to evaluate tofersen via the ongoing clinical trial and real-world evidence generation. We look forward to hearing the perspectives of the committee members on this topic.

DR. MONTINE: Thank you.

DR. FRADETTE: And --

DR. MONTINE: Excuse me.

DR. FRADETTE: Thank you. Yes. Thank you, Dr. Montine.

DR. MONTINE: I don't mean to cut you short, but if I may --

DR. FRADETTE: No worries at all.

Clarifying Questions to the Applicant

DR. MONTINE: Thank you.

We will now take clarifying questions for Biogen. Please use the raise-hand icon to indicate that you have a question, and remember to lower your hand by checking the raised 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 the slide number, if possible.

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

We have approximately 20 minutes for the clarifying questions for Biogen. I would ask my colleagues on the panel to please limit yourself to one question at a time, and we'll just rotate through the group.

I'll start with Dr. Alexander, please.

DR. ALEXANDER: Thanks, Dr. Montine. This is Robert Alexander. My question is in reference to table 12 in the Biogen briefing document, the time-to-event analysis to death

It looks like the most striking difference between early start and delayed start -- and you include the post-withdrawal vital status data -- and my question is, could you speak to how that data was collected and whether you were able to ascertain the status of 100 percent of the patients who withdrew from the study? Thank you.

DR. FRADETTE: This is Stephanie Fradette from Biogen. Slide up, please.

The analysis of incorporating post-withdrawal vital status information was done really in an effort to confirm that we didn't see

something different. We wanted to make sure that with that additional follow-up information, it didn't change what we were observing on the prespecified survival analysis of time to death or permanent ventilation and time to death.

We worked with the principal investigators and site staff at each site to follow up on the vital status of the participants, so this was done through the sites directly, and we were able to confirm the vital status information on all but eight of the participants who withdrew from the study. Thank you.

DR. MONTINE: Thank you.

We move next to Dr. Wilson, please.

MR. WILSON: Yes. Thank you. This is Michael Wilson. I believe this would be for Ms. Fradette. One thing I will note was changing the starting point from time since symptom onset to neurofilament. You explained the NfL well, but what exactly is symptom onset, because it sounds a lot more subjective to me. For example, I had muscle articulations for about 2 years prior to

weakness, so where does symptom onset start? Thank you.

DR. FRADETTE: This is Stephanie Fradette from Biogen. You are absolutely correct that there is a great deal of subjectivity in the assessment of timing of symptom onset. This was evaluated as per the discretion of the investigator. If it was an individual that they had been caring for, of course they had more close contact and were able to speak to that; if not, it was a retrospective evaluation of medical history. So this was, again, per the discretion of the investigator, which introduces variability and subjectivity. This is, in part, why incorporating a measure like neurofilament to control for heterogeneity is more objective and more indicative of disease progression over time. Thank you.

MR. WILSON: Thank you.

DR. MONTINE: Thank you.

Dr. Apostolova, please.

DR. APOSTOLOVA: Liana Apostolova, Indiana University. My question is for Dr. Fradette, and

then I have one later on for Dr. Fanning.

In terms of variability across these heterogeneous mutation carriers, how much was observed? For example, of course it is anticipated that slow progressors will have smaller absolute benefit, functional benefit and otherwise, and faster progressors will have a larger absolute benefit. But with the percent slowing similar or different, based on what you observed and also based on NfL levels at baseline, is there also variability within one type of mutation carriers and aggression of disease of baseline NfL levels?

What might be other factors -- it's a two-prong question -- that might influence variability of response? For instance, in the A5V mutation carriers, there was some variability, of course -- not of course, but are they factors like age and treatment initiation, age at onset, gender? Are those factored in, and how do they influence disease progression?

DR. FRADETTE: This is Stephanie Fradette from Biogen. Firstly, I want to acknowledge the

important point around the variability, even within a given mutation. We've talked about the A5V mutation, which again is perhaps one of the more homogeneous mutations and certainly the best characterized, and even within A5V carriers, we see variability of survival estimates ranging from less than a year to four, and possibly even longer years. So mutation on its own is an important tool to understand and predict what will occur over time, but in the context of a short study, even that falls short.

To answer your question, no specific variable outside of neurofilament is particularly prognostic across the study population because, again, age of onset can differ, and gender doesn't seem to play a role. So we're talking about small numbers here, but we found that neurofilament is the most prognostic, consistent with what our academic colleagues have found and reported in the literature.

Slide up, please. I'm just going to share one example of the differing effects. This is a

rather complicated slide, but you'll see here slow vital capacity on the left-hand side, and on the right-hand side, data from VALOR and its extension study, and you'll see the slower progressing cohorts and the faster progressing cohorts.

What I'll highlight is that in the slower progressing cohorts, as you note, there's less opportunity to show differentiation, but there does appear to be clear benefit, and those individuals that are having slower progressing disease appear to be benefiting in the sense that they appear to be stable over time. So we do observe benefit both in slower and faster progressing subgroups of the population. Thank you.

DR. MONTINE: Thank you.

Dr. Romero, please.

DR. ROMERO: Thank you. Klaus Romero with Critical Path Institute. I also have questions for Dr. Fradette.

On slide 55, you show the overall change from baseline, and then on slide 57, you show the distinction between faster and slower progressors.

Can you comment on any potential contribution of the actual distribution of baseline severity in this score or distinction between slow and faster progressors? Thank you.

DR. FRADETTE: This is Stephanie Fradette. Could we please pull the slide that's being referenced for context? I believe it was slide CE-55.

DR. ROMERO: Fifty-five shows the overall change from baseline, and then on 57 you show the distinction, the further distinction between, quote/unquote, "slow and faster progressors."

(Pause.)

DR. FRADETTE: This is Stephanie Fradette from Biogen.

Could I clarify, are you referring to the Kaplan-Meier curve -- apologies for the delay in pulling the slide -- the survival analysis --

DR. ROMERO: No. No, no, not the survival analysis; the change from baseline results on the score.

DR. FRADETTE: -- of the ALS Functional

Rating Scale.

DR. ROMERO: Correct. I believe it was slide 55 that shows the overall change from baseline, and then slide 57 shows the distinction between slow and faster progressors.

DR. FRADETTE: Great.

Could we please pull CE-11? We'll start by confirming that this is the slide you're referencing. Apologies for the slide number mix-up.

DR. ROMERO: That's ok. They were numbered, so I just went with an overall count of what was in the document.

DR. FRADETTE: Slide up, please.

DR. ROMERO: Yes.

DR. FRADETTE: Okay. Great.

So this analysis, this was the originally prespecified analysis, primary analysis, and this was in the faster progression subgroup defined according to mutation -- so SOD1 mutation type -- and the pre-randomization ALSFRS-R slope decline. So again, we've discussed a bit about the

laws associated with both of those criteria and the fact that neither appear to be particularly prognostic over time; so in retrospect, not an ideal way of defining the primary analysis population.

In contrast, on slide CE-13 -- slide up, please -- these data are in the faster progression subgroup defined according to baseline neurofilament level; so essentially, disregarding the mutation type and pre-randomization slope, and only focusing on the subset of the entire 108 participant population who had a baseline neurofilament level above the median, so associated with faster disease progression.

As I noted, in this subgroup, we actually see mitigation or minimization of the imbalances in baseline characteristics that we observed in the analysis population that was Illustrated on the prior slide; though here, with better control of the heterogeneity, we appear to be seeing greater differences in favor of tofersen. Thank you.

DR. ROMERO: Thank you.

DR. MONTINE: Thank you.

Dr. Gold, please.

DR. GOLD: Hi. This is Dr. Gold, and just a question for Dr. Fradette. I'm looking at slide 82, or where you have the model to evaluate the effect of tofersen in relation to overall survival. I know that you need to pull it up.

What I'm trying to understand is in the context of patients with higher plasma or baseline levels of NfL reviewed as having more severe disease or at risk of faster progression, what was the thought process in the design of the study in terms of effect size? Did you anticipate that patients would have similar both magnitude and speed of response, given the fact that some of these patients had what would be viewed as more extensive disease or more longer duration of disease? I just want to understand how you guys thought about that in the modeling in terms of the natural history and the underlying pathology. Thank you.

DR. FRADETTE: This is Stephanie Fradette.

I'll highlight a couple of points. Firstly, the concept of enrolling or enriching the primary analysis population for a faster progression subgroup, the intent is really that you have more opportunity to see a difference over a short period of time, so similar to what we see in the model. The higher the rate of neurofilament, as indicated in the model, the faster the progression, the more the control or the natural disease progression would decline. So you'd have more opportunity to make an impact or show an impact in a period.

On the flip side, though, it's actually in the slower progressing participants where you'd expect to be intervening early enough to be having a profound effect on their disease. So there's less of a runway, if you will, for the faster progressing individual. This is part of the challenge with enriching study populations, and part of the reason we think it's important to look at the entirety of the study population, all 108 participants, and control for heterogeneity using neurofilament. Thank you.

DR. MONTINE: Thank you.

Dr. Weisman, please.

DR. WEISMAN: Thank you.

My eyes want to see this data set as a delayed-start trial, but I have a concern about survival bias that goes into the open-label extension. I think this is slide CE-7, and the concern is, did rapid progressors drop out of the tofersen early-start arm? So the question is, did those people have NfL levels that were elevated at start? I don't think I saw or appreciated the number of completers at 52 weeks. Thank you.

DR. FRADETTE: This is Stephanie Fradette from Biogen. I'll make a couple points. We don't have the number of completers at week 52 handy, but I think we could likely get that for you, so we'll follow up with that on that point.

What I'll highlight is, as noted, 95 of 108 -- so 88 percent of the overall population -- completed VALOR and rolled into the extension study. And just to give a bit more detail on that, in the delayed-start group -- so

the placebo, the delayed-start group -- that included 19 of the original faster progression subgroup and 13 of that slower progression subgroup. In the early start -- so the green side of the slide -- cohort, that included 33 of the original faster progression subgroup and 30 of the slower progression subgroup. So a vast majority of participants completed and chose to enroll in the extension study.

When we're thinking about the early part of the study and what occurred, you're absolutely correct to highlight that first 52-week period.

Slide up, please. When we look at the Kaplan-Meier curve that was presented, there were a number of events that occurred within the first 52 weeks of the VALOR and extension experience. There were 4 events in the tofersen or early-start arm and one in the placebo or delayed-start arm.

To get to the heart of your question, most of those people -- so nearly all of those participants -- had very quickly progressing disease, very elevated neurofilament levels. I

would say that all but one of the tofersen deaths were associated with disease progression and ultimately respiratory failure associated with ALS.

So we do see sort of this early period of the study, perhaps prior to active biological activity coming into play, where we do have a number of deaths to take into consideration. But overall, we would anticipate that given the number of people that have rolled into the extension -- nearly all of the participants -- [inaudible - audio gap], the treatment arms, that these are interpretable data over time. Thank you.

DR. MONTINE: Thank you.

Dr. Kryscio, please.

DR. KRYSCIO: Yes. It's Richard Kryscio, University of Kentucky. Again, I'm asking a question about slide 71 and 72; a small number of events there, and although most participants, as it was pointed out, went into the delayed-start arms, my concern is when I look at slide number 71, I don't see that Kaplan-Meier curve separating much

until after the delayed start began, and yet we're quoting the log-rank test and also a Cox model, both of which assume proportional hazards. And I was wondering if you did any sensitivity analyses since Kaplan-Meier curves can be compared using other sorts of tests.

DR. FRADETTE: This is Stephanie Fradette from Biogen. Slide up; if we could show that Kaplan-Meier curve, please?

As I noted, and as you note, the differences don't appear to emerge until after week 52. This could be attributable to a couple of factors. One is that we do see an imbalance in baseline characteristics. The tofersen arm appears to be progressing more quickly, so there's more to catch up on, if you will. There's also the time it takes for maximum biological activity to come into play, so it's not totally surprising that we don't see separation until that week 52 period and beyond.

But I'll ask Manjit McNeill to comment on the latter half of your question, and if we could put the slide up, please, for reference.

(Pause.)

DR. FRADETTE: This is Stephanie Fradette from Biogen. We're just reconnecting Manjit McNeill; apologies for the delay.

MR. McNEILL: Hello. This is Manjit McNeill from Biogen, and apologies for the technical hitch. Slide up, please. Thank you.

We did conduct a sensitivity analyses. We performed max combo. On the left here, we have the original log-rank p-values for the Cox regression p-values. For each of the survival endpoints, we looked at time to death or PV time to death; time to death with additional vital status; and time to death and permanent ventilation withdrawal due to disease progression and what we see on the right-hand side, we actually see very consistent results. The p-values are not quite as small as the original Cox regression analysis, but the results are fairly consistent. Thank you.

DR. KRYSCIO: Thank you for answering my questions.

DR. FRADETTE: Dr. Montine, this is

Stephanie Fradette from Biogen. I just wanted to make one final point on this, which is we agree with the comments from the committee that the data for the survival analyses are immature and emerging data, and I want to reiterate that we continue to follow this over time and look to further understand any impact on survival with the completion of the extension study. Thank you.

DR. MONTINE: Thank you very much, and that puts us at time. I know there are additional questions, but we'll have time later in the day for them. We will now break for lunch. We'll reconvene at 12:05 p.m. Eastern time. Panel members, please remember there should be no chatting or discussion of the meeting topics with other panel members during the lunch break. Additionally, you should plan to rejoin around 11:50 a.m. to be sure that you are connected before we reconvene at 12:05 promptly.

Thank you. We are adjourned for lunch.

(Whereupon, at 11:39 a.m., a lunch recess was taken.)

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

(12:05 p.m.)

DR. MONTINE: We will now proceed with the FDA presentations, starting with Dr. Emily Freilich.

Dr. Freilich, please.

FDA Presentation - Emily Freilich

DR. FREILICH: Good afternoon. My name is Emily Freilich, and I am the acting deputy director and cross-discipline team leader from the Division of Neurology 1, for the new drug application for tofersen, for the treatment of SOD1 ALS. I will begin this afternoon's presentation with a brief clinical overview of the available data and considerations for discussion today. This will be followed by additional presentations by our review team, and then I will come back to discuss the safety of tofersen and a few concluding remarks.

As we all know, ALS is a progressive and fatal neurodegenerative disease that is characterized by degeneration of motor neurons, which are responsible for voluntary control of the

muscles. Patients with ALS generally become progressively weaker, losing the ability to move, swallow, and speak. Respiratory muscles are also affected, which leads to respiratory failure and death, generally within 3-to-5 years of symptom onset.

Approximately 5-to-10 percent of all ALS cases are familial, and the mutation in SOD1 is associated with about 20 percent of these familial cases. The SOD1 mutation has also been reported in about 2 percent of sporadic ALS cases. The prevalence of SOD1 ALS is extremely rare, making up about 2 percent of all ALS cases or less than 500 patients living with SOD1 ALS in the United States.

There are over 200 reported mutations in the SOD1 gene that are associated with SOD1 ALS. While the symptoms and disease course are similar to those seen in sporadic ALS, the age of onset, rate of progression, and degree of upper motor neuron involvement may vary with the specific SOD1 variant. For example, as we have heard, the A5V

variant, the most common variant in North America, is reported to have a more rapidly progressive course, with an average disease course of about 1.2 years.

There is significant unmet need in ALS. Approved treatments for ALS are riluzole, edaravone, and sodium phenylbutyrate/taurursodiol. However, these treatments are not a cure, and patients continue to have disease progression leading to death, despite treatment with currently available therapies. There are also no specific treatments approved for SOD1 ALS.

Tofersen is an antisense oligonucleotide that binds to the SOD1 mRNA. Tofersen is administered intrathecally via lumbar puncture every 2 weeks for the first 3 doses, and then every 28 days. Although the pathophysiology of SOD1 ALS is not fully elucidated, it appears that gain-of-function mutations in the SOD1 gene lead to an accumulation of toxic SOD1 protein aggregates, which are implicated in the downstream degeneration of motor neurons. It is proposed that tofersen

will bind to the mRNA and reduce synthesis of SOD1 protein, which will therefore lead to a decrease in toxic SOD1 aggregates. As previously noted, because tofersen is reducing SOD1 protein synthesis, an event upstream of the pathological mechanism for ALS, it is anticipated that any treatment benefit of tofersen would apply to all patients with SOD1 ALS, regardless of mutation type.

To review the regulatory history briefly, the IND for tofersen was opened in 2015, with a phase 1/2 first-in-patient study. In 2019, the study was amended to include part C, the phase 3 pivotal study, after multiple discussions regarding the appropriate primary endpoint and the primary analysis population. In August of 2020, we had a Type C meeting to discuss plans for a study in presymptomatic carriers with confirmed SOD1 mutation. This study is currently ongoing.

In September 2021, we held a Type C meeting to discuss the top-line results of the pivotal phase 3 study, which failed to win on its primary

endpoint. In December 2021, we had another Type C meeting in which the applicant proposed to submit an NDA for accelerated approval based on the results on NfL, in addition to seeing positive clinical trends on multiple analyses. The division agreed with the plan to submit an NDA to allow for more detailed consideration of the data. The NDA was submitted on May 25, 2022.

What is NfL? NfL is the neurofilament protein that is specifically expressed in the cytoskeletons of neurons, including myelinated axons. When neurons are injured or damaged, neurofilaments are released into the interstitial fluid, and then spread to the CSF and the blood. Increased levels of NfL are observed in the CSF and blood in a variety of neurologic disorders. NfL levels are significantly more elevated in patients with ALS compared to many other neurodegenerative disorders.

Elevated plasma NfL levels have been observed as early as 1 year before symptom onset in patients with SOD1 ALS. Recent literature studies

have indicated that NfL levels correlate with disease severity, progression rate, and survival in patients with ALS, which our Office of Clinical Pharmacology colleagues will discuss in more details later.

The applicant proposes NfL as a reasonably likely surrogate endpoint to support accelerated approval of tofersen in SOD1 ALS. Accelerated approval may be granted for a serious and life-threatening disease when a product has an effect on a surrogate endpoint that is not itself a direct measure of clinical benefit, but is instead reasonably likely to predict that clinical benefit.

For us to consider a drug for accelerated approval, the drug must demonstrate an effect on the surrogate endpoint that is reasonably likely, based on epidemiologic, therapeutic, pathophysiologic, or other evidence to predict clinical benefit. The studies used to demonstrate such an effect on the surrogate endpoint must be adequate and well-controlled clinical trials. Additional studies are generally required to

confirm the anticipated clinical benefit.

Should we decide that the available evidence supports the use of NfL as a biomarker reasonably likely to predict clinical benefit in patients with SOD1 ALS to support accelerated approval of tofersen, additional confirmatory evidence of clinical benefit would be required. Given the extremely low prevalence of SOD1 ALS with a small pool of patients available, a second adequate and well-controlled placebo-controlled study in the symptomatic population would be extremely challenging and could take several years.

The applicant has proposed that confirmatory data may instead come from the ongoing phase 3 study in presymptomatic carriers of SOD1 ALS. Unlike the pivotal study we are discussing today, the aim of this phase 3 study is to evaluate if tofersen, compared to placebo, can delay symptom onset in presymptomatic carriers of the SOD1 mutation who demonstrate early evidence of central nervous system disease activity based on a prespecified NfL threshold, but prior to symptom

onset. This study is expected to complete in 2027.

The applicant also has plans to leverage data from the ongoing open-label extension study. They plan to follow patients and assess survival and other clinical outcomes compared to natural history, in addition to the planned comparisons of patients who received tofersen early in the double-blind study compared to the delayed-start patients who received placebo and then switched to tofersen in the open-label extension; there are always limitations, however, to the use of open-label data.

The data available to date comes from a single pivotal study, Study 101C, which was a randomized, double-blind, placebo-controlled study in 108 patients with ALS, secondary to a confirmed SOD1 ALS mutation. Patients were randomized to 2 to 1 to tofersen or placebo for 24 weeks of treatment. Randomization was stratified by categorization as either a fast progressor or non-fast progressor population. The fast-progressor population was based on

pre-randomization slope in the ALS Functional Rating Scale Revised and mutation type. It was hypothesized that it would be easier to detect a treatment effect in the fast progressing subgroup.

The primary analysis was the change from baseline in the ALSFRS-R total score at week 28 in the fast progressor population. Secondary endpoints included the change from baseline to week 28 in CSF SOD1 protein, plasma NfL levels, slow vital capacity, hand-held dynamometry, and time to death or permanent ventilation.

After completion of Study 101C, all patients had the opportunity to enroll in the open-label extension, Study 102, and all patients received active treatment with tofersen. Patients and study site staff remained blinded to treatment received in the double-blind phase. Although the primary objective of the open-label extension was safety and tolerability, biomarker and clinical endpoint data was also collected, and this study remains ongoing.

The results will be further discussed in the

upcoming presentations, but I note that the primary analysis of change from baseline in the ALSFRS at week 28 in the fast progressor population was not statistically significant, although the numbers did trend in favor of tofersen. Exploratory analyses conducted in the full ITT population were also not statistically significant.

Secondary endpoints of SVC, hand-held dynamometry, and time to death also trended in favor of tofersen but were not nominally significant. Among the secondary endpoints, a marked reduction was seen in CSF SOD1 protein levels compared to placebo at week 28 and in plasma NfL concentration compared to placebo, both of which were nominally significant with low p-values. At week 52 in the open-label extension, the applicant compared patients who had received early-start treatment with tofersen in the double-blind phase to the delayed-start patients who had received placebo and then initiated tofersen in the extension study.

As you have heard today, there are different

approaches to the analyses of this data; however, with any analysis method used, we do note that clinical improvement with separation over time was observed in the full randomized ITT population on the ALSFRS, SVC, hand-held dynamometry, and quality-of-life scales, as well as time to death and/or permanent ventilation. Of import, reductions in CSF SOD1 and plasma NfL were also seen in patients after initiating tofersen in the open-label study. The previously seen reductions in SOD1 protein and NfL in the early treatment group were also maintained throughout the open-label extension.

Now you will hear from my colleagues. First, Dr. Tristan Massie will give a statistical presentation with a deeper look at the study results, statistical analysis methods, and the total evidence of effect on the clinical outcomes and the biomarkers. He will also note statistical limitations of NfL as a reasonably likely surrogate.

Then Dr. Xiaohan Cai and Dr. Vishnu Sharma

from the Office of Clinical Pharmacology will present additional background on NfL and SOD1 in SOD1 ALS. They will review the biomarker results in more detail and review the prognostic value of NfL in ALS. Finally, they will review a comprehensive evaluation of the relationship between NfL reduction and clinical function to conclude why NfL may be considered a reasonably likely surrogate to predict clinical benefit in these patients.

Our review includes a multidisciplinary approach to the evaluation of the data. You will hear different interpretations of the same data. Our goal is to present the thinking of the whole team to highlight the strengths and limitations of the available data. I will then conclude with the safety presentation and some concluding remarks.

Dr. Massie?

FDA Presentation - Tristan Massie

DR. MASSIE: Thank you, Dr. Freilich.

Good afternoon. I'm Tristan Massie, a statistical reviewer for this new drug application,

for tofersen in SOD1 ALS. First, I'd like to summarize some of the key points, and then I'll go into more detailed explanations.

As you heard from Dr. Freilich, there are no statistically significant effects on primary or other clinical outcomes in the prespecified analyses. Additional post hoc analyses by the applicant are challenging to interpret due to their data-driven exploratory nature. Limited conclusions are possible from the statistical analyses to evaluate the relationship between tofersen effects on neurofilament in ALSFRS-R and other outcomes.

Here's an outline of the talk. First, I'll examine the evidence for an effect on clinical outcomes in Study 101 Part C as a double-blind, placebo-controlled part, and then for the open-label extension. Next, I'll examine the evidence of an effect on NfL. Third, I'll examine the evidence for NfL as a reasonably likely surrogate endpoint.

Before we talk about the clinical results,

we need to consider the prespecified analysis methods. The final version of the statistical analysis plan prior to database lock was SAP Version 2, finalized on August 14, 2021. Primary analysis of the change from baseline in ALSFRS-R at week 28 was based on an analysis of covariance of joint ranked scores; that is of ALSFRS-R and survival in the mITT population, that is fast progressors.

The analysis was to adjust for the prespecified covariates based on ALSFRS-R, edaravone or riluzole use, and time since symptom onset. Multiple imputation was used for missing data in survivors. Descriptive analyses were to be reported in non-mITT and ITT populations, but no formal hypothesis testing was planned in these populations.

In our summary of the prespecified analysis plan, a sequential testing strategy was prespecified to control type 1 error probability across the following secondary endpoints if the primary endpoint was significant: change from

baseline to week 28 in total CSF SOD1 protein; change from baseline to week 28 in NfL and plasma; change from baseline to week 28 in SVC; change from baseline to week 28 in HHD megascore; time to death or permanent ventilation; and finally, time to death. Secondary endpoint analysis methods for continuous endpoints were similar to those with the ALSFRS-R, except that time-to-event endpoints were to be analyzed by a Cox proportional hazards model adjusted for time since symptom onset, baseline ALSFRS-R, and edaravone or riluzole use.

We've just gone through the prespecified analysis plan for Study 101 Part C, the double-blind part. Here are the corresponding prespecified analysis methods for Study 102, the open-label extension of Study 101 Part C. The primary objective was long-term safety and tolerability. Efficacy evaluation was exploratory. Analysis methods for the open-label extension were similar to those for Study 101 Part C week 28 analysis. The mITT population fast progressors, which was primary for Study 101 Part C, was still

the focus rather than the ITT population since there was no indication otherwise in the prespecified analysis plan for the open-label extension.

Just to summarize the prespecified analysis for Study 101 Part C and the open-label extension, the applicant focuses on additional post hoc analyses. These were detailed in applicant SAP Version 3, dated February 2, 2022. This was finalized after reviewing unblinded, double-blind, and some open-label extension results; for example, ALSFRS-R and survival analyses through week 40 of the open-label extension as reported in a December 2021 Type C meeting to the agency.

These week 40 and survival event outcomes from the open-label period did not change in later database updates or cutoffs. The applicant's additional analyses in analysis plan Version 3 included multiple changes to the prespecified methods, including replacing the time since symptom onset covariate; the baseline NfL focusing on the ITT rather than the mITT population; and changing

the plan for imputation of missing data by replacing since symptom onset with NfL as a covariate in the imputation model, which is a distinct model from the analysis model for the treatment comparison but also affects the results.

Note that post hoc modeling choices can induce substantial bias. Prespecification of covariates is critical for the validity of models. As stated in the FDA draft guidance on covariate adjustment, quote, "Sponsors should prospectively specify the covariates and the mathematical form of the covariate adjusted estimator in the statistical analysis plan before any unblinding of comparative data. FDA will generally give more weight in review to the prespecified primary analysis than to post hoc analyses using different models or covariates."

Now that we've summarized the analysis plan, here are the results of the prespecified analyses of Study 101 Part C. The primary analysis of week 28 ALSFRS-R did not provide evidence of a treatment effect, with a mean difference of 1.2 and

associated 95 percent confidence interval ranging from minus 3.2 to plus 5.5. The analysis in the full ITT population was exploratory, as it was not in the multiple testing strategy. The analysis plan stated that it would have no formal testing. Regardless, the mean treatment difference in the ITT population also did not reach nominal significance.

Here are the corresponding prespecified analyses of key secondary endpoints. There was no evidence of effects on secondary endpoints SVC or HHD megascore. Time to death or permanent ventilation and time to death alone were not formally assessed due to lack of an adequate number of events for meaningful analysis. There was, however, some evidence of effects on the biomarkers SOD1 and NfL, as seen in other presentations in a later slide to come.

Here we see the prespecified analyses of the open-label extension. You can see none of the prespecified analyses were significant. Hazard ratios for adjudicated time to death or permanent

ventilation and time to death event analyses were in the wrong direction; that is numerically favoring placebo in the mITT population but numerically favored tofersen in the overall ITT population. I'll give you a moment to examine the results since there's a lot to take in. The hazard ratios in the fast progressors numerically favored placebo.

Switching back to week 28 of the placebo-controlled Part C, here are the applicant's post hoc analyses of Study 101C for the overall ITT population. They tended to show slightly more favorable results than the prespecified analyses. Note again that the ITT population was to have no formal testing for Part C, and that none of these analyses are nominally significant in the primary fast progressor or mITT population.

Here are the applicant's post hoc ITT analyses of the open-label extension. The applicant's ANCOVA plus MI analyses do not account for 4 tofersen deaths and 1 placebo death before week 52, a trend in deaths which numerically favors

placebo. The post hoc analyses for the open-label extension appears slightly more favorable than the prespecified analyses. Note, however, that in the primary mITT population, none of these endpoints are nominally significant, even with the applicant's post hoc methods adjusting for NfL.

Here we comment on the applicant's post hoc analyses. Some of the analysis changes may have scientific rationale. In particular, there is literature supporting the prognostic ability of NfL, which may support adjusting for NfL in the analysis. The considerably less functional decline on placebo in the fast progressor population than anticipated might suggest focusing on the ITT population. Some of the results may be promising, however, it is likely that part of the reason these analyses were explored is data driven; that is due to lack of evidence in prespecified analyses and search for more favorable results. Data-driven analyses are subject to bias and very challenging to interpret. On the other hand, the prespecified analyses are valid, non-significant, and being

prespecified and valid should be given substantial weight and not discounted.

Next, I'll discuss the evidence of an effect on the biomarker neurofilament light in plasma. The effect on NfL is being considered for reasonably likely surrogacy. Biomarker NfL was to be analyzed by the ratio to baseline rather than change from baseline due to the skewed asymmetric distribution of NfL. This was the second endpoint listed among secondary objectives after the primary endpoint.

There were nominally significant treatment effects on ratio to baseline of NfL for mITT and non-mITT populations, both nominal p-values less than 0.0001. Study 101 Part B also seemed to provide independent support for the effect on this biomarker. Totality of data seemed to provide support for a true effect of tofersen on NfL.

Now that we've examined the effects on clinical endpoints and the biomarker NfL, I'll examine the evidence for NfL as a reasonably likely surrogate endpoint. First, it's important to note

that the evaluation of reasonably likely surrogacy is based on a multidisciplinary approach. Understanding of the disease and mechanism is important.

That said, there were no prespecified analyses assessing this relationship. This may introduce bias. Furthermore, it is challenging to assess whether a drug effect on a biomarker predicts a drug effect on the clinical outcome from a study that did not provide evidence from an effect on the clinical outcome. We'd like to acknowledge that evidence may be limited in a serious rare disease, but evaluation of the evidence supporting reasonably likely surrogacy is important.

Continuing our evaluation of neurofilament as a reasonably likely surrogate, we note that the magnitude of correlation between changes from baseline in NfL and ALSFRS-R in this study is small. As stated in the FDA briefing document, the correlation is minus 0.21 in the mITT population, and this may be influenced by analysis choices; for

example, endpoint selection, scale for NfL, and covariate selection for an adjusted correlation analyses.

Importantly, it should be noted that correlation is necessary but not sufficient to support a candidate surrogate. Additionally, there is uncertainty about strong underlying assumptions of the applicant's causal inference model analysis, as we will see more specifically on the next slide.

Let's look more closely at this causal analysis model. We believe it cannot conclusively establish the causal relationship between tofersen effects on NfL and ALSFRS-R and other outcomes because, for example, the model was developed after unblinding, likely driven by the observed data; therefore, this analysis supports hypothesis generating but not confirming.

Unlike a randomized comparison, the validity of these causal analysis results depends on the form of the model, variables included in the model, and the specific data used to fit the model. Furthermore, the uncertainty of the results depends

on assumptions about the statistical error terms and missing data, which may not be appropriate in the present model. In particular, this is a completers analysis, excluding missing data and even 1 death in the tofersen arm. This model uses counterfactual predictions of NfL progression at day 116 for the drug arm if they had been assigned placebo.

The applicant's implementation treats these predictions as if they were observed outcomes, although predictions by nature always involve additional uncertainty. This should have been accounted for in the analysis, similar to how the primary analysis method accounted for the uncertainty of missing data through the use of multiple imputation. Thus, in this case, without any accounting for the possibility of errors in any of the predictions for every drug [indiscernible] completer, the significance of the estimated causal effect is exaggerated.

This analysis also assumes equal variance across the whole ITT population despite a much

higher observed variance in the fast progressor population as compared to the non-mITT stratum, as was expected at the design stage of the trial, when it was decided to stratify the randomization by fast progressors or others.

Finally, to summarize, there were no statistically significant effects on primary or other clinical outcomes in prespecified analyses. Additional post hoc analyses of clinical outcomes by the applicant are challenging to interpret due to their data-driven exploratory nature. The data do appear to support an effect on NfL. We note again that the evaluation of NfL as a reasonably likely surrogate is a multidisciplinary approach.

The statistical team believes that limited conclusions are possible from the statistical analyses to evaluate the relationship between tofersen effects on NfL and ALSFRS-R, in part, because they were not planned and were data driven, and due to the fact that the study did not show an effect on the clinical outcome among the other issues that were mentioned.

Thank you. That's the end of my portion, and I'll turn it over to my clinical pharmacology colleagues.

FDA Presentation - Xiaohan Cai

DR. CAI: Thank you, Dr. Massie.

I'm Xiaohan Cai, the clinical pharmacology reviewer for this application. In the following section, Dr. Vishnu Sharma and I will present the assessment from the Office of Clinical Pharmacology.

In brief, our presentation focuses on two key messages. First, NfL can be considered as a reasonably likely surrogate for accelerated approval of tofersen for treating SOD1 ALS, based on totality of evidence, and second, the long-term extension study provides support on tofersen's treatment effect.

We'll first provide the background of the two biomarkers, SOD1 protein and NfL, and then provide biomarker results from clinical studies. We'll walk you through multiple analyses supporting NfL as a reasonably likely surrogate for

accelerated approval, based on our three-pronged approaches: mechanistic evidence, prognostic value of NfL, and the relationship between NfL reduction and the clinical function decline. Lastly, we'll present our exploratory evaluation of long-term treatment effect of ALSFRS-R total score.

In Study 101C, SOD1 protein and NfL in the mITT population were assessed as the secondary endpoint. Specifically, as shown in this table, the change of CSF SOD1 protein from baseline at week 28 was ranked as the first secondary endpoint. The change of plasma NfL from baseline at week 28 was ranked as the second. For both biomarkers, pre-dose samples were collected at each visit when the treatment was administered from day 1 to week 28. Comparing to the placebo group, tofersen treatment led to 38 percent reduction of total SOD1 protein in CSF and 67 percent reduction of plasma NfL at week 28 in the mITT population.

To briefly provide a background of these two biomarkers, first I will discuss SOD1 protein. SOD1 protein is universally expressed throughout

the human body and involves the removal of superoxide radicals. In ALS patients with SOD1 mutations, the gain of function with SOD1 mutations is thought as the cause of ALS. The mutations in SOD1 are believed to result in accumulation of toxic SOD1 protein aggregates, which ultimately stimulates neurodegeneration and subsequent clinical decline. The degree of neurodegeneration may be reflected by the neurodegenerative biomarker, such as NfL, which I will introduce in the next slide.

Based on this understanding of SOD1 ALS, the reduction of toxic SOD1 protein in SOD1 ALS patients is thought to be a promising target. As an attempt for lowering SOD1 protein expression, tofersen is an antisense oligonucleotide targeting SOD1 mRNA and inhibiting SOD1 protein translation, including the toxic form.

Next, I will provide what we learned related to NfL. NfL is a subunit of neurofilament proteins. Neurofilament proteins are uniquely expressed in myelinated axons of neurons. As shown

in this illustration, when axonal injury occurs, neurofilaments are released into CSF and blood, allowing their detection in biofluid. Neurofilaments are comprised with subunits with different sizes, including neurofilament light chain, NfL, neurofilament medium chain, and neurofilament heavy chain. Among these, NfL is the mostly studied subunit in neurodegenerative diseases.

Consistent with this understanding, elevated NfL was reported in many neurologic disorders, including ALS, and the elevation of NfL in ALS exceeds those observed in many other neurodegenerative diseases. Recent advancement in NfL assays allowed the measurement of NfL in blood, and the blood level of NfL was reported to be correlated with CSF NfL levels in ALS patients. Emerging knowledge from literature also showed that NfL level correlates with ALS disease progression rates in the survival. To date, NfL has not been used as a surrogate biomarker for drug approval.

In the following few slides, I will present

the details on the biomarker results from tofersen clinical studies. This figure shows the change of total SOD1 in CSF in Study 101C in the ITT population between treatment arms, as shown in this blue line for the tofersen group and the gray line for the placebo group. As shown in the right table, compared to the placebo arm, tofersen led to similar reduction of CSF total SOD1 protein in the mITT and ITT populations.

In these analyses, what you see is the reduction of total SOD1 protein, which is non-specific to the mutated SOD1 protein. Despite this, the total SOD1 protein reduction indicates the knockdown of SOD1 mRNA by tofersen. This is because tofersen is designed to knock down SOD1 mRNA for the mutant and native forms.

Tofersen treatment also led to reduction of plasma NfL in Study 101C. The figure represents the plasma NfL level from week 0 to week 28 in both treatment arms by the mITT population shown in the red color, and by the non-mITT population shown in the blue color. As shown in the right table,

tofersen led to reduction of plasma NfL in the mITT and ITT populations, comparing to the placebo group, although the data from the ITT population are not directly shown in the figure.

We also observed notable difference in baseline NfL plasma level between the tofersen and placebo arms in the mITT population, as shown by comparing the red solid and the red dotted line at baseline in this figure. This suggests some imbalance in baseline plasma NfL levels between the treatment arms in mITT population. The potential implication of the imbalance will be discussed at a later slide.

The result from the long-term treatment extension phase further confirmed tofersen's effect in reducing plasma NfL. This slide shows the plasma NfL ratio to baseline in the ITT population of integrated data from the double-blind and the long-term extension period. In patients who had received placebo in Study 101C, shown as the gray line in this figure, 20 weeks of treatment with tofersen in the long-term extension phase reduced

the plasma NfL level by 44 percent, comparing to the baseline of Study 102.

Based on the results from the last few slides, tofersen showed positive results in reducing total SOD1 and NfL, and its effects in NfL reduction are being considered as a reasonably likely surrogate endpoint for accelerated approval. By regulatory definition, a biomarker that is being used as a reasonably likely surrogate endpoint is an endpoint supported by strong mechanistic and/or epidemiologic rational, such that an effect on the surrogate endpoint is expected to be correlated with an endpoint intended to assess clinical benefit in clinical trials, but without sufficient clinical data to show that it is a validated surrogate endpoint.

In this situation, there is a negative clinical study that failed to show statistically significant treatment effect in the prespecified primary clinical endpoint; however, there is a true drug effect of tofersen to reduce plasma NfL. Although this biomarker is not a validated

surrogate endpoint, it is being proposed as a reasonably likely surrogate to support accelerated approval.

For this purpose, we have multiple analyses to support this argument with three-pronged approaches. First, there is mechanistic support based on the understanding of tofersen's mechanism of action as a targeted therapy and its function effect on NfL. Second, there is scientific evidence supporting prognostic value of NfL in ALS based on our meta-analysis of literature and the regression analysis of Study 101C. Third, our analysis demonstrated the relationship between reduction in NfL and the slowing of the decline on clinical outcomes. From this angle, we'll present our analysis in three parts, a longitudinal change in NfL and ALSFRS-R; correlation analyses; and causal inference analysis.

Next, I will walk you through the first aspect, which is the mechanistic evidence, and my colleague, Dr. Sharma, will walk you through the second and the third aspect. I will start with our

understanding of SOD1 ALS pathophysiology.

Pathologic mutation in the SOD1 gene is the underlying cause of SOD1 ALS. Although the exact mechanism of why the mutated SOD1 gene causes ALS is not clear, the most widely studied mechanism is the mutated SOD1 gene results in toxic accumulation of mutated SOD1 protein. This toxic form of SOD1 protein subsequently leads to neuronal damage and neurodegeneration. Neurodegeneration causes leakage of NfL from damaged neural axons. Consistently, NfL elevation was found in ALS and SOD1 ALS patients. Neurodegeneration and loss of motor neurons also leads to clinical function decline, which is typically assessed by ALSFRS-R.

Next, I will discuss how tofersen works. Tofersen is a targeted therapy targeting the SOD1 mRNA to reduce SOD1 protein translation. The reduced protein translation includes the toxic SOD1 protein that is implicated in the pathophysiology of SOD1 ALS. As mentioned earlier, if tofersen does reduce neuronal damage by lowering SOD1, a reduction in NfL would be the expected outcome.

Based on the clinical biomarker results, reduction of total SOD1 in CSF was observed following tofersen treatment. This confirms the target engagement of tofersen. Consistently, reduction of NfL was also observed with tofersen treatment, and these reflect reduced neuronal damage. This treatment effect in reducing NfL is considered from the pathway of lowering SOD1 protein; therefore, tofersen's effect in reducing plasma NfL is expected to lead to slower clinical function decline.

In summary, the observed treatment effect of tofersen in lowering SOD1 and NfL, along with the understanding of SOD1 ALS pathophysiology, provides mechanistic evidence to support the suitability of using NfL as a reasonably likely surrogate in SOD1 ALS.

Now, I will turn the presentation to my colleague, Dr. Sharma, on the other aspects of our evaluation.

FDA Presentation - Vishnu Sharma

DR. SHARMA: Thank you, Dr. Cai.

Hello, everyone. This is Vishnu Sharma, pharmacometric reviewer. We will now present our assessment for the prognostic value of plasma NfL in ALS. For this objective, we have leveraged data from both the literature and the tofersen clinical program.

This slide summarizes the findings from the meta-analysis of the literature. In this analysis, the relationship of neurofilament with the ALSFRS-R score [indiscernible], disease progression, and survival was collected using PubMed search, and then summarized using the forest plot and random effect model. The forest plot on the right shows the correlation between plasma NfL and disease progression from 12 research studies, along with the overall correlation coefficient of 0.51. This suggested that higher plasma NfL levels are associated with faster disease progression.

Similar analysis was done to evaluate the relationship between plasma NfL and survival using hazard ratio, which suggested that patients with higher plasma NfL have a higher risk of unfavorable

clinical outcomes, which includes death, tracheostomy, and/or permanent assisted ventilation. Overall, evidence from the literature suggests that higher plasma NfL levels are associated with faster disease progression and unfavorable clinical outcome.

The prognostic value of NfL was assessed using the placebo data from the tofersen clinical program. The first objective of the analysis was to confirm if the trend reported for plasma NfL [inaudible - music playing] tofersen's clinical program are [inaudible].

(Pause.)

DR. SEO: Hello. This is Jessica speaking.

Dr. Sharma, we cannot hear you. If you want to check if you're muted in Adobe, please.

DR. SHARMA: Okay. Should I start from the beginning? I didn't realize that I was muted.

DR. SEO: Dr. Sharma, this is Jessica. I apologize to interrupt you. If you could start back at slide 50; that was where we left off. Thank you.

DR. SHARMA: Oh, okay. Thank you for notifying me.

The prognostic value of NfL was assessed using the placebo data from the tofersen clinical program. The first objective of the analysis was to confirm if the trends reported for plasma NfL in the tofersen clinical program are consistent with the literature. For this objective, the relationship between plasma NfL levels and clinical decline across multiple clinical endpoints was evaluated in the ITT population. The three figures in this slide show the correlation between baseline plasma NfL and the change from baseline in clinical endpoints, including ALSFRS-R score, slow vital capacity, or SVC, and hand-held dynamometry, or HHD, at week 28. The findings demonstrate that placebo subjects with higher baseline NfL show faster disease progression across these clinical endpoints at week 28.

Next, we evaluated if the presence of additional prognostic factors other than plasma NfL can affect ALSFRS-R scores at week 28. We see that

two regression methods were used, including linear and lasso regression. The table on the right shows the list of prognostic variables in the analysis, which notably include ALSFRS-R slope and other biomarkers, such as plasma neurofilament heavy chain and SOD1 protein. Both analyses suggest that plasma NfL is a significant predictor for ALSFRS-R change at week 28, even after adjusting other prognostic factors. This analysis may be limited by small sample size, however, these findings are consistent with the findings from the literature based on meta-analysis, and overall supports the prognostic value of plasma NfL in SOD1 ALS.

We will now present our assessment for the relationship between plasma NfL reduction and ALSFRS-R decline in SOD1 ALS using data from Study 101 Part C. This slide shows the temporal relationship between plasma NfL reduction and reduction in ALSFRS-R decline. The figure here shows the placebo corrected mean ALSFRS-R and NfL changes over study weeks. The orange line represents plasma NfL reduction, which appears to

start from week 4 and reach to maximum as early as week 16. Beyond week 16, the mean reduction in plasma NfL are relatively consistent with those at week 16.

The black line represents a reduction in ALSFRS-R decline, which suggests that the mean treatment effect on ALSFRS-R total score started to appear from week 8 and continued to week 28. This could indicate that a treatment effect of slowing of disease progression may not become apparent until several weeks after treatment initiation. Overall, longitudinal changes of plasma NfL and ALSFRS-R suggest a temporal relationship between the tofersen-driven reduction in plasma NfL and reduction in ALSFRS-R decline, which is consistent with the pharmacology of tofersen.

To further understand the relationship between tofersen-driven NfL reduction and a reduction in clinical decline, correlation analysis was conducted The three figure here shows the relationship between plasma NfL reduction and ALSFRS-R changes at week 28 in ITT, mITT, and

populations with higher than median NfL levels of 73 picograms per mL. The gray and blue circles represent data from the placebo and tofersen group, respectively. Correlation coefficients are provided with and without adjustments for other baseline prognostic variables. These prognostic variables were selected based on regression analysis and literature data. The findings suggest that plasma NfL reduction is associated with reduction in ALSFRS-R decline at week 28, and this trend appears to be more prominent in populations with higher baseline NfL levels.

While the correlation analysis can assess the association between plasma NfL and ALSFRS-R decline, it does not directly assess the impact of plasma NfL reduction on ALSFRS-R decline. The applicant has conducted causal inference analysis to quantify the relationship between plasma NfL and ALSFRS-R scores. This slide provides a schematic of the analysis. Briefly, the change in ALSFRS-R scores at week 28 in treatment group was modeled as a linear function of three components, which

includes natural disease progression, drug effect through NfL pathway, and drug effect through non-NfL pathway.

In terms of data, the natural disease progression in treatment group was informed by subject baseline characteristics and the placebo data for ALSFRS-R total score and plasma NfL. The plasma NfL data from the placebo group was used to project plasma NfL change at week 16 in treatment group. This estimated plasma NfL change in treatment group was then used to inform both natural disease progression and drug effect to the NfL pathway. The treatment data for plasma NfL and other baseline variables was used to inform drug effect to NfL and non-NfL pathways, respectively.

The causal inference model was used to evaluate the relationship between plasma NfL reduction and treatment effect on ALSFRS-R decline. This figure shows the relationship between plasma NfL reduction at week 16 and ALSFRS-R decline at week 28 for tofersen-treated subjects after adjusting for model-predicted placebo effect. The

estimates of slope from a univariate linear regression and causal inference model are also provided in the figure.

Of note, the slope estimated from causal inference model is slightly shallower than a univariate linear regression slope as it adjusts for other potential prognostic factors such as ALSFRS-R total score, plasma NfL, percent-predicted SVC, and ALSFRS-R slope. Overall, treatment effect on ALSFRS-R total score appears to be associated with NfL reduction even after adjusting for other potential prognogstic factors. Of note, while the NfL change at week 16 was used in the analysis, similar results have been shown at other time points as well, including week 20, week 24, and week 28.

The causal inference model was applied to evaluate a clinical trial scenario where prognostic variables were balanced between placebo and tofersen groups. The figure on the left provides a simplistic representation of the analysis. Imbalances in baseline characteristics may affect

the treatment effect. For instance, there was a difference of around 30 [indiscernible] units, on average, in baseline NfL between two groups in the mITT population. The causal inference model can address these imbalance issues by creating a matched control group based on individual baseline characteristics and observed placebo response. This matched control is expected to predict the disease progression of tofersen-treated subjects as if they have received the placebo.

The results from the analysis are shown on the right. The orange circles represent matched placebo group for tofersen-treated subjects, the gray circles represent the placebo group, and the blue circles represent the tofersen group. The treatment effect, after adjusting for baseline prognostic factors, is projected to be 3.8 units instead of the observed treatment effect of 2.1 units.

There are additional aspects to be considered regarding the analysis presented here. The analysis utilizes data from the ITT population

to provide the largest number of patients and broadest range of NfL changes and ALSFRS-R changes. Of note, similar findings have been observed in the primary or mITT population. These analyses were based on study completers only, accounting for 90 percent of the enrolled patients. The limitation must be recognized, including the post hoc nature and a small size study.

Also, although a small size study, this was a randomized comparison, so correcting for a post hoc imbalance, here plasma NfL, must be considered with caution. Overall, the analyses suggest that plasma and NfL reduction appears to be associated with reduction in decline or clinical endpoint.

To summarize, the regulatory definition of a reasonably likely surrogate endpoint is defined as an endpoint supported by strong mechanistic and/or epidemiologic rationale, such that an effect from the surrogate endpoint is expected to be correlated with an endpoint intended to assess clinical benefit in clinical trials, but without sufficient

clinical data to show that it is a validated surrogate endpoint.

Considering the regulatory definition of a reasonably likely surrogate endpoint, we have presented various analyses that assess the biological plausibility of the relationship, prognostic value of plasma NfL, and the relationship between tofersen-driven NfL and clinical decline. Overall, based on the totality of the data, plasma NfL appears to be a reasonably likely surrogate endpoint for SOD1 ALS subjects.

We would now like to present our understanding and interpretation of the long-term study. This study evaluated treatment effect on ALSFRS-R total score using integrated data from Study 101 Part C and Study 102. This slide shows the longitudinal changes in mean plasma NfL in ALSFRS-R in study completers until week 52. The figure on the left shows the mean plasma NfL reduction over study weeks. The blue line shows the data from the early-start group and the gray line shows the data from the delayed-start group.

The subjects in the early-start group received tofersen over the entire 52 weeks, while the subjects in the delayed-start group received the placebo until week 28, and then received tofersen after week 28. Overall, both the early-start and delayed-start group showed similar NfL reduction upon initiation of tofersen treatment. The figure on the right shows the ALSFRS-R change over study weeks, which suggested numerically less decline in ALSFRS-R total score in early-start group as compared to delayed-start group. We will discuss these ALSFRS-R results in more detail in the next slide.

With regard to the primary efficacy endpoint, that is the ALSFRS-R total score, if one assumes that tofersen has no treatment effect, starting treatment 28 weeks earlier or later would not be anticipated to impact disease progression. In that case, the ALSFRS-R data between the early-start group and placebo delayed-start group would overlap, as seen in the first 8 weeks. Nevertheless, the consistent separation on ALSFRS-R

between the two groups from week 8 and onwards appears to further support the potential treatment effect of tofersen. Of note, this analysis was based on study completers only, accounting for nearly 80 percent of the enrolled patients. The percentage of dropout is also balanced between early-start group and delayed-start group, with similar range of ALSFRS-R change at the last visit.

Also, we acknowledge that after week 28, the trial entered the open-label phase, and all patients started to receive the same active treatment; however, the enrolled patient, site staff, and vendors were still blinded by the initial treatment assignment, even after entering the open-label phase. So we believe it is unlikely that the initial treatment assignment would significantly affect the ALSFRS assessment in the open-label phase.

To conclude, we would like to summarize our presentation with three key points. First, tofersen treatment reduces neural injury by lowering SOD1 protein levels as reflected by the

reduction in total CSF SOD1 protein and plasma NfL in SOD1 ALS patients. Second, plasma NfL is specific to neuronal injury and appears to be a reasonably likely surrogate endpoint for SOD1 ALS, based on the following: mechanistic support based on disease pathophysiology and the pharmacology of the tofersen; demonstration of the prognostic value of plasma NfL in ALS; and relationship between plasma NfL reduction and ALSFRS-R total score.

Lastly, in the long-term treatment study, the early-start tofersen group showed a numerically less decline in ALSFRS-R total score from week 8 onwards as compared to the delayed-start group, which supports the potential treatment effect of tofersen. This concludes our presentation, and I will now hand it over it to Dr. Emily Freilich for the other aspect of the submission.

FDA Presentation - Emily Freilich

DR. FREILICH: Thanks, Dr. Sharma.

I will now give an overview of safety in the tofersen development program. The safety database consisted of 147 patients, including 116 patients

who were treated for more than one year, which is adequate for this rare disease population. The most common adverse events noted were pain, myalgia, arthralgia, fatigue, and an increase in CSF white blood cell count.

There was permanent discontinuation due to adverse events in 6 percent of the tofersen group compared to 0 percent in the placebo group. Those adverse events leading to discontinuation, that occurred in more than one subject, were respiratory failure, respiratory arrest, and ALS worsening, which are all related to underlying disease progression.

There was a single death in the double-blind treatment period in the tofersen treatment group. This death was due to congestive heart failure, and the patient had heart disease prior to treatment. There were no deaths in the placebo arm in the double-blind phase.

Serious adverse events occurred in 18 percent of tofersen-treated patients and 14 percent of placebo patients. These were also

largely related to underlying disease progression. There were, however, serious neurologic events that occurred in patients receiving tofersen that did not occur in patients receiving placebo.

Four patients in either Study 101C or Study 102 reported serious adverse events of myelitis. One patient developed paraplegia and sensory loss in the legs, with MRI findings of an inflammatory myelopathy from lumbar to cervical cord. This patient discontinued tofersen and responded to treatment with steroids and plasma exchange, and had symptom resolution within 2 months.

Another patient also had findings of transverse myelitis, which responded to steroids. This patient was ultimately diagnosed with neurosarcoidosis as the etiology of the transverse myelitis, and did later withdraw from the study due to ongoing risks. The other two patients who reported transverse myelitis were asymptomatic, and the myelitis was found on MRI, which was done for elevation in CSF white blood cell count. Both of

these patients continued in this study, one after brief treatment interruption. A fifth patient in the expanded access program also reported myelitis, leading to discontinuation.

There were two events of radiculitis that were also noted. These patients were able to continue on treatment with complete resolution of symptoms. The first patient presented with low back pain with elevation of CSF white blood cells and protein and was diagnosed with a transient lumbar radiculitis that resolved after 1 day. The other patient developed back and side pain with numbness in the feet, and was diagnosed with radiculitis with enhancement of cauda equina roots on MRI imaging. This patient continued treatment, and symptoms resolved after several months.

There were results of one patient each who reported an episode of aseptic meningitis or chemical meningitis. There were also additional reports of non-serious elevations of white blood cells in the CSF. The patient with chemical meningitis did discontinue treatment and had

complete resolution of symptoms within 2 weeks. These adverse events have also been reported with other intrathecally administered treatments.

There were also 4 patients who reported a serious adverse event of either papilledema or increased intracranial pressure. None of these events led to permanent discontinuation. One patient also had concomitant aseptic meningitis and asymptomatic myelitis that had been previously described. Increased intracranial pressure, as well as hydrocephalus, have been reported with administration of other intrathecal ASOs and appear related to the route of administration.

Generally, tofersen via intrathecal administration was well tolerated. Other known class effects of ASOs that are given intravenously, such as thrombocytopenia, kidney toxicity, and hypersensitivity, were not seen in the safety database thus far. The risk for serious neurologic events may be related to the route of administration. The majority of serious adverse events resolved without permanent discontinuation;

however, patients and providers need to be aware of the potential for these serious neurologic events. If approved, these risks should be described in labeling; however, given the severity of ALS, none of these risks appear to preclude approval.

In conclusion, SOD1 ALS is a very rare, serious, and life-threatening disease. Tofersen is a targeted therapy. The noted reductions in biomarkers are suggestive of target engagement, as well as potential downstream effects. The pivotal study failed to detect a statistically significant treatment effect; however, we note that all clinical outcomes trended in favor of tofersen, and separation over time was noted between the treatment groups. The pivotal study also had its limitations, including that the rate of disease progression was much lower than predicted, leading to the study being markedly underpowered. The study was also likely too short to duration to detect a clinical treatment effect, if there is one, given that it took 16 weeks to achieve maximum reduction in NfL levels.

The observed changes in NfL and clinical outcomes may be adequate to support approval in one of two pathways for this rare disease. The ALS guidance for industry states, "The statutory standards for effectiveness apply to drugs with ALS, just as the standards apply for all other drugs. However, FDA has long stressed the appropriateness of exercising regulatory flexibility in applying the statutory standards for serious disease with unmet medical needs, while preserving appropriate assurance of safety and effectiveness."

The first approval pathway under consideration today is accelerated approval, which can be considered if the observed reduction in plasma NfL levels in tofersen-treated patients is reasonably likely to predict clinical benefit in these patients. Additional confirmatory evidence of clinical benefit would be required.

Given the exceedingly low prevalence of SOD1 ALS, the seriousness of the disease, and the substantial unmet need, we would also like input

from the committee members on whether the combination of the existing clinical data from the phase 3 study and the available open-label extension study results, accompanied by the reduction of SOD1 and NfL, provide convincing evidence of the effectiveness of tofersen in the treatment of patients with SOD1 ALS, which would support full approval.

That brings us to the discussion and voting questions for today's meeting, which are shown on this slide and which we will be discussing later. Thank you. We can now take clarifying questions from the committee.

(Pause.)

DR. SEO: Hi. This is Jessica.

Dr. Montine, if you're speaking, we cannot hear you. You may be muted. If you could look at Adobe Connect and unmute, please. Thank you.

DR. MONTINE: Hi, Jessica. Can you hear me now?

DR. SEO: Yes, Dr. Montine. We can hear you now. Thank you.

Clarifying Questions to FDA

DR. MONTINE: My apology. I don't know exactly what happened.

Thank you, Dr. Freilich. Thank you, FDA team. We have 20 minutes for clarifying questions for the FDA. Please use the raise-hand icon to indicate that you have a question, and remember to clear the icon 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 the 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 that we can move on to the next panel member. And as we did before, please limit yourself to one question so that we can cycle through everyone, and time allowing, we'll return for follow-up questions.

So the order in which individuals have

raised their hands, first is Dr. Romero, please.

DR. ROMERO: Thank you. Klaus Romero with the Critical Path Institute. I'd like to thank the clinical pharmacology reviewers for such a clear presentation, but my question is for Dr. Tristan Massie.

The numbering of the slides you presented doesn't seem to correspond with the PDFs. I'm going to give you the title of the slide, the one titled, Limitations of Applicant's Causal Inference. In that slide you have a bullet that indicates the potential concern that I don't understand. It reads, "Model developed after unblinding, likely driven by the observed data."

What I don't understand is the fact that every modeling percentage here was data driven, so why is that characteristic of the modeling presented voiced as a concern? And the second part of the question is, for some of the modeling done, one of the key things that you need to know is to which arm each data point belongs. So again, a characteristic of the modeling presented requires

an unblinding of the data, so I don't understand why that is listed as a concern. Thank you.

DR. FREILICH: Thank you, Dr. Romero. This is Emily Freilich. I will turn to Dr. Massie to answer your question.

DR. MASSIE: Hi. This is Tristan Massie. It's just noted that data-driven models are hard to interpret and prone to bias. That's the only reason because this model was developed with knowledge of the data and not prespecified; that's a lesser limitation, though. The other limitations we noted, such as excluding missing data and 1 death in the drug arm, are bigger, I think, issues with the model.

DR. ROMERO: Thank you. Yes, that addresses the question, but still, I'm not sure that that should be voiced as such a strong concern, but thank you.

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

Dr. Apostolova, please.

DR. APOSTOLOVA: Liana Apostolova from

Indiana University. Thank you so much for the FDA presentations. They were very enlightening, and they did answer my first question, which I had for the Biogen representatives, which was regarding side effects and which side effects caused discontinuation of the person, and were patients rechallenged, so all of that was answered.

I'm wondering if NfL levels were actually measured in those who permanently discontinued treatment, and what did those show.

DR. FREILICH: Thank you, Dr. Apostolova for that question. I will see if our colleagues in clinical pharmacology can answer a question about which patients the NfL levels were measured in.

DR. ABUASAL: Hi. This is Bilal Abuasal. I'm the clin-pharm leader. Our understanding is that the NfL measures were for patients who remained in the study, not --

(Crosstalk.)

DR. APOSTOLOVA: So those who permanently discontinued drugs, you didn't follow up with plasma NfL.

DR. ABUASAL: No, we don't have these data, no.

DR. APOSTOLOVA: Okay. Thank you.

DR. MONTINE: Thank you.

Dr. Alexander?

DR. ALEXANDER: Thanks, Dr. Montine. It's Robert Alexander from Banner. My question is for Dr. Cai and Dr. Sharma from the clin-pharm group. I thought you made a pretty strong case that NfL could be a reasonably likely surrogate, but there's a ceiling on the NfL reduction effect of tofersen, and there's a limitation as to how much of the ASO you can safely give intrathecally.

Do you have any insight into whether the magnitude of the effect that tofersen can deliver is sufficient to provide a clinically meaningful response in this population? Thank you.

DR. ABUASAL: Hi. This is Bilal Abuasal. I'm the clin-pharm team leader, and I can start, and my colleagues can add.

Just to clarify, when you refer to the ceiling effect, are you referring to the fact it

reached a plateau and stayed there?

DR. ALEXANDER: No, I'm just saying there's a maximum dose that you can deliver, so that sort of sets the limit as to how much NfL reduction can be achieved, so it's not like you can increase the dose further. So what evidence is there that that magnitude of reduction is sufficient?

DR. ABUASAL: Right. What we can say is that the dose that was tested is the only dose that was evaluated in the study. We only have information about the 100-milligram dose that resulted in around a 67 person reduction in NfL. The sponsor did submit some information suggesting that higher exposure may not have resulted in higher clinical benefit; however, based on what we know about the prognostic value and what a 67-person reduction would mean, it seems substantial enough to likely suggest a treatment benefit, and that was further supported with a correlation analysis presented by Dr. Sharma.

I would like to ask Dr. Sharma to add if he wants to comment more on this one.

DR. SHARMA: This is Vishnu Sharma from pharmacometrics. Yes, 100 milligrams was a maximum dose that was tested in this clinical program. Applicant has done PK/PD modeling for NfL, where they have shown that increasing the dose to 150 and above would not increase the NfL reduction further; however, we do not have data to support that. So at this time, 100 milligrams is the maximum dose, and around 60 percent reduction is what we are looking at.

DR. ALEXANDER: Thank you.

DR. MONTINE: Thank you.

Dr. Weisman, please.

DR. WEISMAN: Thank you. I'm interested to see if there's any evidence that shows that unblinding events could have occurred at the site level in either the randomized-controlled portion of the trial or the open-label extension, specifically, the myelitis and radiculopathies, but also the CSF that showed an imbalance in white blood cells. Thank you.

DR. FREILICH: This is Dr. Freilich. Thank

you for that question. We do not have any evidence of unblinding, but it is reasonable to consider that the CSF changes may have allowed some of the investigators to be suspicious of the treatment effect. But that might be a question for the applicant in terms of how that was handled at the investigator level, but we did not see that as a potential limitation, and clearly would not have impacted the NfL levels.

DR. MONTINE: Thank you.

Dr. Gold, please.

DR. GOLD: Hi. This is Dr. Gold; a small question for the clin-pharm group on the FDA. I didn't see any data presented. There's a Study 233HC101, which is in the briefing document, page 21, that talked about the distribution of tofersen in the CNS. It's a small study. My recollection is there were 8 subjects, five of which were censored because of a GCP problem.

Are there any data on CSF exposure response? I'm trying to understand if the argument here is that NfL is potentially surrogate. Do we have data

on exposure response, not just dose response?

DR. ABUASAL: Right. This is Dr. Bilal Abuasal. I'm the clin-pharm team leader, again. The sponsor submitted exposure-response information, and Dr. Sharma should be able to provide more information on that. I think there is some exposure-response relationship that Dr. Sharma --

DR. GOLD: And maybe just to clarify, plasma exposure alone [indiscernible] muscle, and I'm very curious if there's any sort of CSF or CNS exposure-response relationship. Thank you.

DR. MONTINE: Thank you.

This is Tom Montine. If I could direct a question, please, to Dr. Massie. You made the important point that correlation is necessary but not sufficient for surrogacy, and then pointed out that correlation between plasma NfL concentration in the ALSFRS-R was small, and I believe you showed minus 22. Yet, the graphs that were shown by the clin-pharm group seemed to suggest that the relationship between NfL concentration and ALSFRS,

SVL [ph], and even the hand strength, that those correlations were stronger in their presentation.

I believe this is an important point, and I'm not quite sure why in your analysis it appears so much lower.

DR. ABUASAL: Can you point to the slide number, please, so everyone is aware which slide you're talking about?

DR. MONTINE: I, unfortunately, didn't note the slide number. I apologize. It was a slide with three graphs, all showing a relationship between plasma NfL concentration, and then each of those clinical endpoints.

DR. ABUASAL: Okay. I think it's slide 60. If you can pull up slide 60 to make sure we pull up that slide, slide 60 or maybe slide 61.

DR. MONTINE: If I may, while you're pulling that, the graphs you presented show, at least what appeared to me, a discrepancy between the stat group and the clin-pharm group on the strength of the correlation, the neurofilament levels and then the ALS score.

DR. ABUASAL: Right, right.

First, if you can help us pull up the slide; maybe slide 55 he's referring to, so that we're sure that everyone --

DR. MONTINE: Thank you.

DR. ABUASAL: -- that's the one.

I think, Dr. Sharma, you can speak to that.

DR. SHARMA: Please. This is Vishnu Sharma, pharmacometrics. Is this the slide or you were talking of 55, slide 54 or 55? Is this the slide you are questioning?

DR. MONTINE: This is the slide.

DR. SHARMA: For sure. Okay. Yes, I can walk over this slide again.

This slide essentially shows the prognostic value of NfL, using placebo data from the tofersen treatment program, and the objective here is to show the prognostic values. So we looked at key clinical endpoints, one, primary, ALSFRS total score, and two, secondary, slow vital capacity and hand-held dynamometry. As you can see, consistent with the literature, subjects with higher baseline

NfL have more disease progression in terms of all three clinical endpoints. That's what we have shown on this slide.

DR. MONTINE: Great. Thank you.

So if you take, for example, the slide on the left that has the Pearson r minus 0.65, I believe what Dr. Massie presented was that the correlation between these two ledgers, the plasma NfL and the ALSFRS-R, was [inaudible - audio gap], and I was trying to understand why it's minus 0.65 here and minus 22 in the other.

DR. SHARMA: Sure. I think I understand your question now.

Can you go to slide 55, please? I think it's 55 or 54, which has the plot. I think that's where --

DR. ABUASAL: I think it's slide -- if you can move --

(Crosstalk.)

DR. SHARMA: Or I can just simply state it [indiscernible]. Maybe I can try from my end.

There are two different aspects here. The

slide I just showed, or I just explained, is essentially showing the relationship between baseline plasma NfL and disease progression, where we see there's a good prognostic value for ALS.

In this slide, rather than baseline NfL, we are showing plasma NfL reduction on the X-axis, so this one is basically showing the relationship between plasma NfL reduction and disease progression, so that is the difference. I believe -- and I'll defer to our stats colleagues -- this is the relationship we are mentioning.

As you can see in this slide, what we are showing is the relationship in three different populations, ITT, mITT, and the population with baseline NfL more than medium NfL. What is noticeable here is that while in the ITT, or even in the mITT, if we compare this with the population with higher NfL levels, one can see that prominent or better correlations have been observed in the subjects with higher baseline NfL.

But maybe, I think, for the ITT population,

it may be affected by disease heterogeneity, and that's why we see some correlation of around 0.2, according to the analysis, but I will ask the stats colleagues to comment more.

DR. ABUASAL: Right. I don't know, Tristan, if you're connected back. We lost connection. Some other stats colleague can help answer until Tristan reconnects.

DR. MONTINE: I see. Thank you. I get it. Thank you.

Mr. Wilson, please.

MR. WILSON: This is Michael Wilson, and this is for Dr. Massie. I guess I'm less concerned with what was prespecified versus [indiscernible]. I'm more concerned with which analysis is more accurate. If the trial were to start over, do you have thoughts on what is a more appropriate baseline, whether it be NfL or time from symptom onset? Thank you.

DR. FREILICH: Thank you, Mr. Wilson.

Dr. Massie, are you back online to answer that question?

DR. MASSIE: Yes. Hi. This is Tristan Massie. The problem is that the analyses that are not prespecified were subject to bias, and the NfL-adjusted analysis is susceptible to this bias. Thus, as stated in my presentation, such post hoc analysis results are hard to interpret, and you have to change the population from mITT to ITT also before you get trends in the right direction, both of which induces bias. So at the end of the day, we have to rely on the prespecified analyses, which aren't susceptible to this bias and are valid.

DR. MONTINE: Thank you.

Dr. Apostolova, you have a second question, please?

DR. APOSTOLOVA: Sorry. I had to unmute. Yes. Liana Apostolova, Indiana University.

I have a question about the graphs that are displayed here. From what we saw, the changes over time in NfL and ALSFRS-R were shifted in time, and also were non-linear. Would the Pearson coefficient be the most appropriate method to analyze potential association between the change

over time in such variables? I'm not a statistician; I'm just asking, out of curiosity. Thank you.

DR. FREILICH: Dr. Massie, would you like to answer that first?

DR. MASSIE: Hi. This is Tristan Massie. I don't think the correlation is necessarily the best way because as we noted in our presentation, correlation is necessary but not sufficient to validate surrogate endpoint, and the correlation I had quoted was here in the central figure on the slide.

DR. APOSTOLOVA: But given that the two measures are shifted in time, because it takes time for a functional outcome to occur after a biomarker measure or biomechanistic measure responds, shouldn't that be taken also in consideration? How should we read the data here?

DR. FREILICH: I'm going to let Dr. Sharma respond as well.

DR. SHARMA: This is Vishnu Sharma, pharmocometrics reviewer. Here, we are essentially

looking at two variables. It is not, I would say, as a time component in that, so what we're really looking at here is the plasma NfL reduction at week 16 and ALSFRS-R change from baseline at week 28.

Now, as you see the data, any plot of this, you can tell we have used Pearson's correlations here, but if you really see, even the data looks similar to linear, but we have looked at other methods as well, like Spearman and all others as well. Irrespective of which method is used, the trend, or I would say the association with plasma NfL reduction, ALSFRS-R change stays the same. So we have looked at other metrics as well, and here we have shown only one metric. Thank you.

DR. MONTINE: Thank you.

Are there any additional questions from the panel for the FDA team?

DR. ROMERO: I did raise my hand again. This is Klaus Romero with the Critical Path Institute.

DR. MONTINE: Please go ahead.

DR. ROMERO: Thank you.

I want to make sure that we don't get lost in the terminology. One thing is a fully validated surrogate; another thing is a reasonably likely surrogate. And even though, yes, the class, we're focusing on the primary analysis of a trial is sound, those primary analyses link to prespecified questions. But I want to satinize [ph] in this conversation the responsibility that we all have to make sure that we maximize utility of every precious data point, including the data points that are collected in such a difficult environment in rare diseases.

So the linkage between a biomarker in what has been observed in the data as a post hoc analysis, yes, it is understood as a post hoc analysis; yes, it is understood as a data-driven model, yes, but you can make the argument that [indiscernible] mechanistic models are even harder to interpret, but you still need sometimes those [indiscernible] mechanistic models to make sense of data. So I just wanted to make that comment so

that we don't get lost in the terminology. Thank you.

DR. MONTINE: Thank you.

Are there questions --

DR. FREILICH: Thank you.

Dr. Montine, sorry. This is Dr. Freilich. Dr. Buracchio had a follow-up point to one of the earlier questions.

DR. MONTINE: Please. Excuse me for interrupting.

DR. BURACCHIO: Sure. Hi. Yes, this is Teresa Buracchio. I just wanted to comment on Mr. Wilson's comment earlier about what would be the right model, an analytical model, going forward. I think if we were going to design a study -- or I should say if the sponsor was going to design a study going forward and asked us for our advice on it, that I do think that we would give strong consideration to including NfL as a covariate and, obviously, we probably would want a longer duration of the study as well.

But I do think that just because these are

post hoc analyses and exploratory that the sponsor has presented, that it's still reasonable to consider them because there is a good scientific rationale for why they have chosen these methods. So I can't say exactly what we would advise going forward, but I do think that their proposals are reasonable to consider in future studies.

DR. MONTINE: Thank you, Dr. Buracchio.

Any further questions from the panel for the FDA?

DR. BURACCHIO: I see Dr. Levin would also like to make a comment.

Would you like to go ahead, Greg?

(No response.)

DR. BURACCHIO: If you're speaking, Dr. Levin, we can't hear you.

DR. MONTINE: Well, perhaps while we're waiting, Dr. Weisman had raised his hand again.

Dr. Weisman, please.

DR. WEISMAN: Yes. I'd like to get the statistical person to comment on slide 63 because it seems like there are two camps within the FDA;

the statistical analysis doesn't look good, lots of biases and confounders, and the pharmacology, which is better.

Dr. Massie, can you comment on slide 63, and tell me why these lines, that's seemingly diverged, are biased and should be not seen?

DR. MASSIE: This is Tristan Massie. I believe the analysis on the slide is a completers analysis, excluding about 20 percent missing data. There was 20 percent missing data, and in addition, there were 4 deaths in the drug group and one on placebo up to week 52, which are totally ignored in this analysis. In fact, the analysis imputes missing scores after death for those 5 patients. So I think it's a misleading analysis.

DR. WEISMAN: It's biased because of dropouts.

DR. MASSIE: And also, we think they present just one standard error away from the mean, where you need to look at two standard errors in order to discern differences that are significant.

DR. WEISMAN: Okay. Thank you.

DR. MONTINE: Thank you.

We're just about at time, so one final question from the panel?

(No response.)

DR. MONTINE: If not, then we're going to take a break. We'll now take a break until 2:10. Panel members --

DR. ABUASAL: If you don't mind, can Dr. Sharma make a final comment?

DR. MONTINE: Of course. Please go ahead.

DR. ABUASAL: Dr. Sharma? He can clarify --

(Crosstalk.)

DR. SHARMA: Okay. That's fine.

This is Vishnu Sharma, pharmacometric reviewer. The figure that we just showed, actually it's coming from observed data. So what you're really looking at is mean -- or using study completers only. However, the number of subjects who completed the trial, or study completers, was around 80 percent, and this percentage of dropout was balanced between both two groups. We have also

evaluated the ALSFRS-R score of these subjects at the last visit, as well as their baseline NfL, and both of these ALSFRS, as well as NfL, were in the similar range across these two groups.

Now that being said, additional analyses were also done by the applicant, where they have used missing data -- imputed data, and used some other alternative models. We can also perhaps refer to those. We can also refer to the applicant to comment on those analyses if needed. Thank you.

DR. ABUASAL: Right. Thanks, Dr. Sharma.

If I can add something, these three presented for the observed data are to show trends of treatment benefit to supplement our analysis on the totality of events, evidence based on the biomarker and all the data that we've shown before. So this is kind of supportive, and it's not designed in a way to analyze the statistical significance. They are shown to outline the trends of treatment benefit and not the statistical significance. We just wanted to make that clear. That's why we presented these data.

DR. MONTINE: Thank you.

DR. FREILICH: Thank you.

Dr. Montine, sorry. This is Dr. Freilich again. I just wanted to see if we had Dr. Levin audio working now for a brief comment.

DR. LEVIN: Can you hear me? Can you hear me now?

DR. BURACCHIO: Yes.

DR. FREILICH: Yes.

DR. BURACCHIO: Yes, we can hear you.

DR. LEVIN: Okay. Thank you. Sorry about that.

This is Greg Levin, Office of Biostatistics, FDA. I just wanted to follow up on the question in discussion earlier. I think there was a question about which of the analyses is more accurate, the prespecified analysis or the post hoc ones, for example, that additionally adjust for baseline NfL. I just want to emphasize that I think if prespecified, either one of these would be accurate, either one would be valid, and we would more than encourage, as Dr. Buracchio noted,

adjustment for baseline covariates that are prognostic to increase precision. This is strongly recommended and encouraged in our draft guidance.

However, once the analysis is unblinded, given that there are always a variety of alternative valid analyses that would be accurate if prespecified, it becomes more challenging to interpret the ones that have been selected after looking at the data, and I think this is the point that Dr. Massie was making. There are always a variety of alternative analyses that would be valid if prespecified. Once you have the opportunity to look at the results of those and determine which one you are going to emphasize after seeing the data, it becomes more challenging to interpret the results of the ones that are emphasized, even if there is scientific rationale.

I just want to emphasize that point. If prespecified, they would both be accurate. There would just be differences in precision. But once the data are available, it becomes more challenging to say that data-driven analyses are accurate.

DR. MONTINE: Thank you. Thank you so much for the clarification. Thank you to all the members of the FDA for their presentations.

We're now at time. We'll take a 15-minute break. Panel members, please remember that there should be no chatting or discussion of the meeting topic with anyone during the break. We will resume in 15 minutes at 2:10 p.m., if we're on break. Thank you.

(Whereupon, at 1:56 p.m., a recess was taken.)

Open Public Hearing

DR. MONTINE: We will now begin the open public hearing session.

Both the FDA and the public believe in a transparent process for information gathering and decision making. To ensure the 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

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, product, and if known, its direct competitors. For example, this financial information may include the sponsor's payment of your travel, lodging, or other expenses in connection with your participation in the meeting.

Likewise, FDA encourages you, at the beginning of your statement, to advise the committee if you do not have any such financial relationships. If you choose not to address this issue of financial relationships at the beginning of your statement, it will not preclude you from speaking. The FDA and this committee place great importance 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 to 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 very much for your consideration.

I'll also add, before we begin, there's a limited time allotted to each speaker. As I said, we are very grateful for your insights. We have 26 people registered to speak. We must keep on time, or else those towards the end of the list simply won't have any time at all. So I don't mean to be rude, but once the clock hits zero, I would please ask you to stop and conclude your comments. After a few seconds go by, I really need to interrupt; again, not to be rude, just to ensure that everyone has a fair chance to speak.

So with that, will speaker number 1 begin by stating your name and any organization you are representing, for the record.

MS. BURELL: Hi there. My name is Alison Burell, and I'm not representing anyone.

(Pause.)

MS. BURELL: I will go ahead and get started at this time, if that's alright. Again, my name is Alison Burell, and I would like to thank you for allowing me the opportunity to speak in regards to my family's experience with tofersen. I do not have any financial relationship with Biogen or this drug.

Today, I will be speaking on behalf of my husband, Cory Burell, who passed away March 7, 2019 at the age of 35, a little over two years after diagnosis. Cory was an incredible father to two boys, a supportive husband, a wonderful guy and friend to so many. If Cory was here today, I know he would be speaking directly to this committee.

In 1997, Cory lost his dad to ALS, a year after diagnosis. Unfortunately, Billy was adopted, and we have no family history beyond Billy. In 2015, Cory experienced a wakeboarding accident which caused droplets. He was told initially that it would take time for the nerve to regenerate, and even though his dad had ALS, they were certain he

did not. After 18 months of no improvement and increased symptoms in other limbs, Cory's ALS was confirmed in February, and confirmed as SOD1 in March of 2017.

At time of diagnosis, symptoms were primarily in lower limb, utilizing a cane to walk while breathing, and speech was not impacted. Cory made it his purpose to find a trial that could help those with ALS, bring awareness, and advocate for ALS in a cure. The Biogen trial immediately came on his radar as the trial he wanted to participate in; however, it was not until fall of 2017 that he was able to enroll in this trial.

In addition to the risks that were involved in participating in any clinical trial, there was additional burden, as he had to travel from North Carolina to Johns Hopkins for appointments; however, this trial gave Cory hope that he could eventually get the drug, and hopefully it would help slow down the disease progression, hope that his dad never had.

After every lumbar puncture, Cory would have

a migraine by the time we got home, and that would last for a minimum of 3 days. Cory was able to manage the migraines, and the lumbar puncture itself never bothered him. From November 2017 to April 2018, during the initial trial phase, Cory lost the ability to walk and drive, the ability to transfer from wheelchair by himself, and 50 percent of his lung function. He relied on a non-invasive ventilator, Hoyer, and power chair to move; however, he still had the ability to talk, eat, and decent use of upper limbs.

Cory began open label of June of 2018 and continued this through February of 2019. After starting open label, it appeared that the drug substantially slowed down the rate of his progression. Over the course of the last 6 months, we saw substantial improvement in the loss of his respiratory lung function and progression overall. Cory received 11 doses of drug in the open label between June and February. Unfortunately, a perforation caused by his feeding tube caused infection in his overall body and resulted in him

being trached in February 2019. Our last visit to Johns Hopkins was after he was trached on February 27 2019. His body was fighting to recover from surgery of his perforation an infection had caused. His body was weak.

Tofersen gave Cory time with his boys, making memories and showing them to never give up no matter what obstacle you are faced with. I ask you to please recommend your approval in support of tofersen. Can you please give hope to others with SOD1? I ask you on behalf of my family, on behalf of Cory, and all of those with SOD1. Thank you again for this opportunity to speak.

DR. MONTINE: Thank you.

Will speaker number 2 begin by stating your name and any organization that you are representing?

MS. GREEN: Good afternoon. My name is Raziel Green, and I'm representing myself.

Good afternoon, and thank you for giving me the opportunity to speak about my experience with tofersen. I became symptomatic in 2014, muscle

weakness, and falling, tripping, and a couple of neurologists couldn't figure out what was wrong. A couple of years later, close to 3 years, three [indiscernible] neurologists later, I was diagnosed with SOD1.

Shortly after my diagnosis, I received a call from my doctor, and he informed me about this trial. By May 2017, I went to screening in Boston and began treatment. Once I started receiving tofersen, my symptoms started to stabilize. It was only during the washout period that I noticed I became weaker. I went from holding someone's arm to needing a cane full time, but once back into receiving tofersen, I've been stable since, and it has slowed the progression of my condition, and to this day, I continue to do my daily activities independently.

Tofersen has prolonged my life, and I enjoy living and spending time with my family and friends. I am thankful that I was given a chance to be a part of this trial, and support the approval of tofersen. Thank you.

DR. MONTINE: Thank you.

Will speaker number 3 begin by stating your name and any organization you represent, for the record?

MR. MELMEYER: Thank you for the opportunity to speak to you today. I am Paul Melmeyer, vice president of public policy and advocacy at the Muscular Dystrophy Association, and we serve all individuals with neuromuscular diseases, including ALS, in a variety of ways, including advocating for the accelerated development of more and better therapies for the neuromuscular disease patient population. I have no financial relationships to mention.

MDA does not participate in product-specific advocacy, and thus will not make a specific recommendation on this drug. Instead, I will outline the flexible regulatory approach we expect the FDA and this advisory committee to utilize when considering this and all rare neuromuscular diseases therapies. We are grateful that the FDA has emphasized exercising appropriate regulatory

flexibility, including in the published briefing document and in Dr. Buracchio's opening statement, and we encourage this committee to remember the following three key points when evaluating this and all other neuromuscular therapies.

First, we urge the FDA to flexibly and consistently use the accelerated approval pathway for approving rare neuromuscular disease treatments when proving clinical effectiveness in heterogeneous, often slowly progressing, neuromuscular diseases is not possible.

We understand that some have called for more infrequent use of the accelerated approval pathway, but to do so may essentially halt all possibility of safe and effective treatments reaching some neuromuscular diseases, an absolutely unacceptable result. We urge the agency to continue to flexibly apply the accelerated approval pathway in rare neuromuscular diseases while utilizing the authorizations pertaining to postmarket confirmatory trials enacted by Congress last year.

Second, we are grateful for FDA's

reiteration of the various ways substantial evidence of effectiveness can be demonstrated within its briefing document, stating, quote, "Our regulations allow for 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," end quote.

The briefing document further quotes [indiscernible] in its 2019 guidance, stating, quote, "The second trial may be infeasible in certain rare disease settings where the limited patient populations preclude the conduct of a second trial. In these cases, the substantial evidence of effectiveness would typically be provided by a single trial plus confirmatory evidence," end quote.

FDA has demonstrated several recent examples of using confirmatory evidence to support approval of neuromuscular disease treatments, and we encourage the agency to continue to do so.

Finally, we remind the FDA and the advisory committee of flexibilities outlined in the ALS Developing Drugs for Treatment Guidance, including that the, quote, "FDA will consider patient tolerance for risk in 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 standard for drugs for serious diseases with unmet medical needs while preserving appropriate assurance of safety and effectiveness," end quote. Thank you for the opportunity to testify today.

DR. MONTINE: Thank you.

Will speaker number 4 begin by stating your name and any organization that you represent, for the record?

DR. BUCELLI: Hi. My name is Bob Bucelli. I want to thank the organizers and members of the advisory committee for providing me the opportunity to speak to you all today. I'm a professor of

neurology at Washington University School of Medicine in St. Louis. I co-direct the Wash ALS center alongside Tim Miller, whom you've heard from already today, and I serve as a site PI for seven Biogen sponsored ALS clinical studies, four of which our tofersen related. I've also served on advisory boards for Biogen as a paid consultant.

I want to emphasize that I'm coming to today's meeting to provide my perspective as a clinician that cares for patients with neuromuscular disorders, including ALS, in the inpatient and outpatient setting. Over the last seven years, I've managed 24 SOD1 ALS participants in tofersen-related clinical programs at our site. It's nothing short of an honor and a privilege to care for these individuals and their families, and I want to thank all of them for their selflessness and sacrifice in making this important meeting today a reality, particularly the participants that are no longer with us.

My esteemed colleagues in the neuromuscular section at Wash U have nearly 165 years of

cumulative experience in caring for thousands of ALS patients. Despite all of this experience, I was the first among our group to witness an ALS patient stop progressing and then improve, a patient treated with tofersen. The number of tofersen-treated participants who are improving at our institution is now at six and counting.

Given the limited time, I'll limit my discussion to neurofilaments as therapeutic biomarkers in ALS and other neuromuscular disorders. In keeping with what was presented earlier today, our lab has found that reductions of serum NfL correlate with clinical improvement in a vast array of treatable neuromuscular disorders, and of the 20 ALS patients with serial NfL measurement at are clinical lab, only four have shown reductions in neurofilaments, and all four of those patients are receiving tofersen through the expanded access program. The clinical correlate for these reductions in two of these individuals has been highlighted earlier by Tim Miller.

In keeping with the comments shared by

multiple parties earlier today, our experience with tofersen-treated participants also suggests that the clinical benefits of tofersen are often delayed until 3-to-4 months after initiation treatment, an observation that lines up with VALOR as a negative trial. That stated, knowing what we now know about this drug, and much of which has been powerfully outlined during today's meeting, another placebo-controlled trial of tofersen informed by the shortcomings of the VALOR design is, in my opinion, no longer ethical.

As recent as five years ago, I was perhaps naïve and didn't think I would see an ALS patient stabilize or regain motor function in response to a therapeutic intervention during my career. Witnessing the dramatic benefits that tofersen has had on individuals living with ALS has fundamentally changed my outlook and my approach to the evaluation and management of ALS patients. Accordingly, as a neuromuscular clinician, I'm haunted by the idea of practicing in a world where tofersen is not available for patients diagnosed

with ALS due to mutation SOD1. With that, I'll conclude and thank the organizers, again, as well as the committee and other participants for the opportunity to speak.

DR. MONTINE: Thank you.

Will speaker number 5 begin by stating your name and any organization you are representing, for the record?

DR. AJROUD-DRISS: Good afternoon. My name is Senda Ajroud-Driss. I'm a neuromuscular neurologist, and I see ALS patients at the Les Turner ALS Center at Northwestern Medicine in Chicago. I'm a site investigator for the VALOR extension study, as well as the expanded access program for tofersen. I also have served on advisory boards for Biogen. But during this call, I would like to focus on my clinical experience.

I've spent the past 20 years of my life caring for patients with ALS. I have followed many, many, many families with ALS due to the SOD1 mutation. I know that you are aware of how devastating the diagnosis of ALS is, but can you

even imagine what it means to have a familiar form of business where you do not have just one patient and a family, but many, and in every generation?

Can you imagine having the most common SOD1 mutation in the U.S., the A5V mutation, the one with the most rapid progression and the shortest survival, where disease duration from onset to death is only 18 months?

Can you picture me sitting across the exam room in my clinic from such patients, telling them just that? Not only do I have to deliver this horrible news, but I also must tell them that their children when they grow up, they will have a 50 percent chance of getting the disease, and if they do, it will follow the exact same progression, only a few months to live.

Now fast forward a few years later. Having cared for the parent, I am now sitting across the same example from one of the children that inherited the mutation and now is showing symptoms. If you thought that my first discussion with a parent was difficult, this one I'm about to have

will be excruciating comprehension. I would have to look at them in the eye and deliver the same diagnosis with perhaps the same support and symptomatic treatment. I will have to tell them that despite all the progress in medicine and science over the past decade, there's nothing I can do for them.

But wait. Maybe the discussion with the affected son or daughter does not have to go this way. Maybe at this time, I can offer this family hope, hope in the form of a new treatment, that if used early enough, can slow down this horrible progression and give my patients some time, time to celebrate a milestone, a life event, or for even better treatment to be available. Having been involved in this trial, I was able able to see firsthand how my patients had already defied the odds, and a few of them are living longer than anybody in their family every day. I urge you to recommend approval of tofersen for the treatment of SOD1 ALS. Thank you.

DR. MONTINE: Thank you.

Speaker number 6, will you begin by stating your name and any organization that you represent, for the record?

MS. HADDAD: My name is Cassandra Haddad, no conflicts, and I'm representing myself. You've heard the science. Here is a humanity. I am not a scientist; I'm a mom.

Today I'm asking for your help. For at least seven generations, my family has been decimated by SOD1 AV5, a particularly rapid genetic variant. Our ALS body count so far is 33. My grandfather died in just 12 months, after being given the infamous medical advice to just go home and get your affairs in order. This same dismissal has been given to ALS patients for the last 153 years, and is still being given today.

More recently, my uncle was diagnosed, and for the first time our family had hope because he was able to enroll in this VALOR trial. His ALS progression not only stopped, but he started to have some improvement. Then COVID hit, and his trial site decided to stop treatment. He begged to

continue, knowing he would rather take his chances with COVID than ALS. He rapidly regressed, and when the trial site resumed, he died a short time later, surviving about 18 months, a record in our family.

Next was my mother. Her symptoms started the day her brother died. We raced to get her into the same trial, but it was full. As my mom progressed and we knew death was inevitable, to know that there was a treatment out there for our specific gene was absolutely inhumane. And then a miracle happened. Biogen announced an expanded access program, and a wonderful neurologist helped my mom be the first person to get tofersen through EAP.

While we had waited for access to this life-saving drug, her ALS had progressed, but she still had some mobility and could find meaning and purpose by making memories with her family. With tofersen, she had stabilized, and we had new hope. Ultimately, after a year of tofersen and COVID complications, she decided her fight was over, and

we spent three amazing months together with hospice. I know tofersen gave us that precious time together. My mother lived 25 months. In my family, that is a miracle, the miracle of having access to a drug that specifically targets our genetic mutation and extends our lives.

During her journey, I had genetic testing, and rather than having to hope for an EAP or being scared about a long diagnostic delay, I have the blessing of being in the ATLAS trial and being monitored for a rise in the biomarker NfL or ALS symptoms, which would trigger the early intervention of tofersen. We all know that early intervention leads to better outcomes.

Without tofersen, I have zero chance of survival, and I have no hope. And just like I watched my mother die, my children will watch me die, perpetuating the multigenerational trauma that is inherent to genetic ALS. My twins are just six and I am 42. With an average age of onset of 49 years old [indiscernible], I can't help but wonder how much time do I have left with my

children.

Tofersen is a life-sustaining and memory-making medication. We need treatment. We need hope. Please help us by approving this drug and making ALS a livable disease. Today you have the power to help me and my family's legacy of death. Thank you.

DR. MONTINE: Thank you.

Speaker 7, will you please begin by stating your name and any organization you are representing, for the record?

MR. LAWRENCE: Yes. My name is Peter Lawrence, and I'm not representing any organization. Members of the advisory committee, thank you for the opportunity to address you regarding my experience with the drug tofersen. As we all know, ALS progresses differently in afflicted individuals; however, I feel I'm in a unique situation to speak, however, just for myself and not for any others afflicted with this terrible disease.

Since 1978, I have witnessed five members of

my family -- my mother and sister, two brothers and a nephew -- all pass away from SOD1, all while relatively following the same pattern: complete loss of mobility and muscle use roughly after the first year, and then in need of breathing and feeding assistance shortly thereafter, with death following roughly within 2 years of diagnosis.

I was positively diagnosed in November of 2020 and accepted in the tofersen phase 3 trial at MGH the following month. At that time, I started to experience the rapid loss of mobility, especially in my lower body. I went from walking without assistance to a wheelchair in 4 months. While it is unknown if I was receiving a placebo or the trial drug, my loss of muscle and strength in my lower body slowed down significantly by June of 2021 when I entered the open-label phase. I started to level out and maintain mobility and strength, especially in my upper body.

My condition has not changed significantly since then. There's been well over 2 years since my diagnosis, and I'm still independent in many

daily functions. I do not require medical assistance with breathing or swallowing, and show no indication of needing one any time soon. I can cut my food, chew and swallow, drink and sleep without being elevated, and speak clearly.

This far into the diagnosis, my family members affected by SOD1 had already passed or were bedbound and dependent on medical devices to keep them alive. Without any doubt in my mind, I believe that my current condition is due to the effect of tofersen. I am hoping that my story will help you further recognize the benefit of tofersen and its critical value for the ALS community and finally help the brain break the chain of SOD1. I pray for all of those who are suffering or carrying this awful disease. Thank you very much.

DR. MONTINE: Thank you.

Speaker 8, will you please begin by stating your name and any organization you are representing, for the record?

MS. SWIDLER: Good afternoon. My name is Jean Swidler. I'm the founding chair of Genetic

ALS and FTD: End the Legacy, the first organization dedicated solely to the interest of the genetic ALS and FTD community. I have no disclosures. I personally am a C9orf72 carrier, but today I'm speaking on behalf of the group and our whole community.

Let's take a moment and think about SOD1 ALS. As we've heard from many of the speakers so far, and I'm sure many after me, let's just think of the horror of this mutation in families. The average age of onset for SOD1 ALS is 49. Parents' average age for a mother is 28; for a father it's 31. Do the math and realize that children grow up without their grandparents, and parents leave the world while their children are still young adults or children. Think of the intergenerational trauma that this provides to people. This is horrible, and if we can interrupt this chain of sadness, we must do what we can.

Tofersen should not be judged on 6-month data. As has been fully explained, the full suppression of this SOD1 protein wasn't achieved

until halfway through the 6-month trial, and the nadir of neurodegeneration not achieved until the end of the 6-month period. I respect the job of the FDA staff that need to present their [indiscernible] and to warn against post hoc analysis.

Knowledge does not reveal itself in the confines of the clinical trial only. We now know what NfL means, and we know that ALS is a neurodegenerative disease. Significantly slowing excessive neurodegeneration is the goal of any ALS intervention. Tofersen achieved this dramatically. We must approve tofersen, and we must accept neurofilament light chain as a surrogate marker for ALS and FTD clinical trials. Thank you so much.

DR. MONTINE: Thank you.

Speaker number 9, will you please begin by stating your name and any organization you are representing, for the record?

MR. FALIVENA: My name is Larry Falivena, and I'm representing myself as a person with SOD1 ALS. I've no financial connection with the

sponsor.

Although there's no history of ALS in my family, a genetic test showed that ALS is caused by an SOD1 mutation. Thankfully, I was able to enroll in the VALOR study, and I'm still participating in the open-label extension; so actually, my data is part of what you're currently reviewing.

Just last month, I visited with my local ALS clinic at Duke, and my doctor, occupational therapist, physical therapist, and pulmonologist were all pleasantly surprised that my measurable results hadn't changed in almost a year and a half, and these results are supported by the measurements taken during my visits in the open-label extension.

My real life functional experience and the data show that tofersen has contributed to the stabilization of my ALS. As has been mentioned numerous times, a disease like ALS affects more than just the patient, particularly one with a genetic cause. I have two teenage boys, and because of my genetic form of ALS, they now have the risk of developing this disease. So not only

do I have to deal with the disease myself, but there's also the ever-present burden of knowing I may subject them to this disease as well.

Knowing there's the treatment for this form of ALS, and better yet, potentially a way to prevent this disease from ever manifesting itself, would not only save me, but give my children the freedom to live their lives without this weight on their shoulders. Tofersen is the opportunity to break the cycle of genetic ALS for families who've been devastated by this disease for generations, and while I've been lucky to participate in the trial and the open-label extension, others haven't had this opportunity.

I note [indiscernible] a young man of two must make an 8-hour drive every month to receive treatment via expanded access, and while it's certainly extending his life, it is a drain on his quality of life, which is why this drug needs to be approved and made readily available to everyone who needs it. I ask that you review the effectiveness of tofersen with the latitude that's required for a

fatal disease, as well as understand the higher tolerance of risk this patient community is willing to accept.

This is a horrible disease with very few options for treatment and no cure, so any opportunity to slow or stop this disease is a win for the entire ALS community, even if it only affects a small percentage of patients. Recent developments and new treatments like tofersen are [indiscernible] to ALS becoming a livable disease instead of a fatal one.

There's hope in the community that we could be the first generation of ALS patients to see effective treatments. I ask that this committee recommend the approval of tofersen so that we can take the next step in making that hope a reality, and changing the course of families' lives for generations to come. Thank you.

DR. MONTINE: Thank you.

Speaker number 10, please begin by stating your name and any organization you are representing, for the record.

MS. BECKER: Hi. My name is Connie Becker, and I am speaking on behalf of my family today.

As I said, my name is Connie, and I'm honored to be with you all as we discuss ALS, tofersen, and my family, the Payne family. After more than 100 years of living with this horrific disease in our family, we finally have a glimpse of hope. Our family has an E100G SOD1 mutation. We have lost 22 family members and now have four living with it. My Grandpa Payne was one of four of 6 brothers to pass away from ALS. From those 4 brothers, every generation after has had family members with ALS.

On the attached slide, you'll see the faces of a few of our family members that fought hard to live, but ultimately succumbed to this horrendous disease. I wanted you to see their faces and not just hear their statistics. The next slide are the four living with ALS now. This is our new reality we believe, in large part, thanks to tofersen.

Our family played a role in the discovery of the SOD1 gene, and we have been studied all over

the world in hopes of a different answer, better treatment, et cetera, but nothing was available. There truly was no hope. From the moment we were old enough to ask questions, it was drilled into our heads that we were never to be tested. There is nothing that can be done about it, so why know? We should live our lives and let whatever happens happen; that we will support each other as best we can, and carry on. We all learned to be a caretaker for each other no matter how young or old, with many in our family losing a parent at a very young age.

We come to you today for approval of tofersen. My family is trying to live with ALS. They deserve to have a hand in their future, in their children's future, and grandchildren. If they give their approval to take tofersen, their only chance right now, that should be enough for the FDA to give theirs. Death is a certainty without the opportunity to try. They deserve the opportunity to try. We need to give them some of their power back to live. Tofersen must be

approved.

Here are some of our families' powerful testimonies and what tofersen means to them. My cousin living with ALS, 43 years old, diagnosed March 2022. "I was 18 when my dad passed away from ALS at 37 in 1997. I feel my ALS has slowed down due to taking tofersen. I've noticed my voice has gotten stronger, and having been in a wheelchair for months, I can now walk short distances that I haven't done since before tofersen. I want my story to be different than my Dad's."

Cousin Jean, positive, 33 years old. "ALS is like a speeding car blowing through a red light as you watch it charge towards you. You can't stop it. But wait; tofersen can slow it down, delay it, and even stop the inevitable destiny we face. Please, please put yourself in my shoes, in our shoes. We are dying waiting for things to change. Make tofersen happen."

Cousin Jean, positive, 58 years old. "The decision to be tested came solely after seeing one of my cousins last July. She is currently

receiving tofersen and looks so healthy more than 2 years after diagnosis, which is truly amazing. This gives me hope for when and if I start to display symptoms, not only for myself but for my children. I want to stress that finally having something so positive relating to an ALS diagnosis is a game-changer for how I go about living my life."

In conclusion, before tofersen, my family and the ALS Community had no hope, only immense pain and sadness. We need you now more than ever. Tofersen must be approved. Thank you.

DR. MONTINE: Thank you.

Speaker 11, please state your name and any organization you are representing, for the record.

DR. RENKO: Good afternoon. My name is Caroline Renko, project manager at PharmedOut, a rational prescribing project at Georgetown University Medical Center. I have no conflicts of interest.

We urge this committee to reject tofersen. The drug simply does not work. In this phase 3

clinical trial, tofersen failed when compared to placebo. You will hear a statement today from advocacy groups in support of approval, but please keep the conflicts of interest of these groups in mind. The patient advocacy groups supporting this drug, which were created or co-authored for industry, defend ineffective or unsafe drugs, and express views more closely aligned with industry than public health.

I AM ALS published a guide to persuade this committee to vote on emotions rather than evidence. The guide reflects industry's planned perspectives [indiscernible], urging patients and families to explain, quote, "how urgent it is to bring new treatments to market," people living with ALS, and the tremendous potential this has for moving all science forward. The guide calls tofersen safe and effective, and says, quote, "This drug will be the first that can slow, or even stop, the most aggressive version of ALS." This committee knows that those statements are false. The phase 3 clinical trial failed to meet its primary endpoint,

and 1 in 14 of all treated participants experienced serious neurological harm.

I AM ALS fails to disclose where they receive their funding, but their sentiments echo those of the ALS Association, which has received hundreds of thousands of dollars from Biogen. The ALS Association notes that they provide funding for the development of tofersen and may receive financial payments under undisclosed circumstances. The association provides grants to pharmaceutical companies and notes that those grants include payback provisions for other financial interests.

So it should come as no surprise that the ALS Association argues it would not be ethically or operationally possible to run a new larger and longer randomized trial. In fact, it would be unethical to unleash a treatment on a vulnerable population when it has no proven benefit and has proven harms. The argument that ALS cannot wait any longer for treatment is specious. Waiting is the scientific, ethical, and rational response to a treatment that is no better than placebo.

If this drug is approved, it is likely to be prescribed off label. Approving tofersen before any clinical benefit has been shown will not only put an effective drug on the market, but will ensure that a larger market is exposed to a highly questionable drug.

The Les Turner ALS Foundation, also funded by Biogen, writes in their comments that patients need hope, but false hope by these efficacy groups is worse than no hope at all. Industry-funded efficacy groups will pressure you, the committee, to approve this sponsor's drug, but we urge the committee to make decisions based on data, not hope. ALS patients are desperate for an effective treatment, but, unfortunately, tofersen is not it. Patients and their loved ones deserve better. Thank you.

(Pause.)

DR. SEO: Hello. This is Jessica.

Dr. Montine, if you're speaking, we cannot hear you. Can you check if you're muted?

DR. MONTINE: Excuse me, Jessica, and excuse

me, Speaker 12.

Speaker 12, would you please begin by stating your name and any organization you are representing, for the record?

MS. NORTH: Hi. My name is Abby North, and I thank you for the opportunity to speak today and provide you with qualitative evidence that does support tofersen's success. I am not representing any organization.

After my mom was diagnosed with ALS in 2018, it felt like every week or month a loss in function necessitated a quick search for adaptive equipment and inevitably a learning curve for our family to navigate. Her lower body function went quickly. Over the course of months, she went from cautious steps, to a cane, to a wheelchair, to a stairlift. And while that rapid decline was not surprising to our family, where the SOD1 mutation has taken lives for many generations, it instilled an immediate grief to what she had lost and the fear toward what she would lose next.

When we came across the VALOR study in 2019,

we finally found hope. During the initial placebo-controlled phase of the trial, and now in the open-label extension, her hand and arm mobility decline has significantly lessened, if not leveled. Her lung function and her ability to speak and swallow, the facets we were most concerned about, have yet to be impacted in a serious way. She continues to eat normal food, to dress herself, adjust yourself in bed, read, call friends, shower, and use a standard non-electric wheelchair.

As you well know, the ALS Functional Rating Scale was a primary endpoint of the original trial, measuring aspects of physical function; 48 is a normal score. When my mom was diagnosed in July 2018, she had a score of 40, which declined to a score of 20 [indiscernible] by May 2019 when she received her first dose. As of March 2023 at her last visit, her score was 27, a decline of only 2 points in 4 years.

I am a researcher by trade and understand the need to find statistical significance, but it is without a doubt, because of the efficacy of

tofersen, that my mom is still able to live alone and independently five years into her diagnosis. For my mom and for her daughter and caretaker, who is carving out her own teacher, I feel indebted to tofersen, Biogen, and the incredible team at Wash U, particularly Dr. Bucelli, whom we heard from today, responsible for providing my mom unmatched quality of care, even through a pandemic.

However, my mom is one of the lucky few to access such a powerful and effective treatment, a treatment we only wish her mother and relatives that came before could have tried. Surviving 5 years into a diagnosis, let alone maintaining the resemblance of a normal and healthy life, is inconceivable to many in the ALS community.

Until there is a cure for ALS, a halt to rapid progression, as others have spoken to, should and is the best possible scenario. By approving this drug, you will be getting precious time back to families facing intergenerational trauma and protecting people like me, a priceless and critical affordance. I urge you to recommend this drug

based not just on hope but on qualitative evidence and observations like mine before more precious lives are lost to genetic ALS. Thank you.

DR. MONTINE: Thank you.

Speaker 13, would you please begin by stating your name and any organization you are representing, for the record?

MS. DANGEL: Hi. My name is Blaine Dangle, and I'm currently participating in the tofersen EAP. I have no disclosures.

I recognize to the advisory committee that this is not an easy position to be in, having to reconcile a complex data set with the needs of patients suffering from a uniquely cruel and hopeless disease, so I want to thank you for being here today and for giving me the opportunity to share my experience.

After 3 years of limping and a progressive leg weakness that was making it impossible to take stairs, walk short distances, or even stand for more than a few minutes at a time, I received an ALS diagnosis in September of last year. I don't

think that there's any way to describe how it feels to get news that you have a terminal illness at 38, with soul-crushing new truths that I would be stripped of my independence and die with so much of my life left unlived.

On the same day as my diagnosis, my neurologist, Dr. Harms, suggested the tofersen EAP. He said I shouldn't expect my legs to get any better, but that it might slow down my progression, or in a best-case scenario, stabilize my symptoms. As a skeptic, I wasn't convinced that tofersen would work, but it's not like I had a variety of treatments available, so I went forward with it anyway.

What I'm here to tell you today is that I was wrong, and so was Dr. Harms. Three months after my first dose, the ever ethical Dr. Harms informed me that he would no longer be authorizing a permanent handicap parking pass; instead he would only be granting me a temporary one because according to my strength scores, I was improving, and suddenly it seemed possible that I might not

need a pass at all. I started to protest. This was my one silver lining, and I was quickly met with the joking suggestion that I could always stop taking tofersen.

Since that first dose, I am doing things that I could not do and had accepted that I would never do again. My limp has gone from an obvious disability to barely perceptible. I can go into my office again because I'm able to get up and down the subway stairs. I was able to visit a friend's new baby on a third-floor walk-up. I no longer need to pull up a stool to cook; I can stand the whole time. I can shower without my shower chair, although I'll admit, I might keep the shower chair. It's pretty luxurious.

At last, when I read the public comments from a tofersen study coordinator about her patients sending videos of themselves making functional gain, I am that patient at Columbia. My poor study coordinator has been on the receiving end of so many clips of me climbing on and off the Peloton by myself; marching steadily up steps

without holding handrails anymore; screenshots of my ever-improving walking asymmetry scores on my Apple watch.

I know what my future looks like without tofersen. It looks like my mom. Like me, her symptoms started in her leg and spread until she could no longer walk at all. Now her hands are so weak that she can barely open a bottle of water. But because of tofersen, my story can be different from my mom. It is unequivocally changing my life.

I allow myself to hope that because of this drug I will no longer have a terminal illness, and as has been said, a manageable chronic condition. I will live, I will walk, I will have the life I imagined for myself. I know I'm just an N of 1, but I respectfully request this ADCOM include my experience in the totality of evidence that you're weighing here today, for me, for my mom, for all ALS patients with an SOD1 mutation. Thank you for your time.

DR. MONTINE: Thank you.

Speaker 14, would you please begin by

stating your name and any organization you are representing, for the record?

MR. SNOW: [Indiscernible]. My name is Chris and Kelsie [indiscernible].

MS. SNOW: "I am not representing any organization and have no financial affiliation. Today stands to be a seminal day for the future of my family. The past has not been kind to us. Today, March 22nd, my father Bob should be celebrating his 73rd birthday; instead, he died in 2018 at age 68, 9 months after his death diagnosis of A4V SOD1 ALS, as aggressive a form of the disease as exists; [indiscernible] his experience with missing a limb, the diagnosis, the rapid withering, and the certain death came as anything but expected.

"In 2004, ALS took my father's younger brother, David, at 48, also in 9 months. In 2013, his youngest brother, Brad, died at 52; again, just in 9 months. Most devastating, in 2016, we buried Brad's son Matt. It was 18 months, but was gone at age 28. In June 2019 at age 37, my turn came. My

right hand and forearm went fast.

"A neurologist with decades of study of families with ALS, including my own family, gave me one year to live. 'What do I do,' I asked. 'Do what brings you joy,' he said, and join this clinical trial. Within minutes, I had a screening visit scheduled for a spot in phase 3 of the tofersen VALOR study. One month later, I received my first dose. Fifty spinal injections later, I am evidence that early diagnosis and early dosing of tofersen can make a massive difference.

"On the 1-year anniversary of my diagnosis, when I should have died, I instead kicked football 47 yards. On the 2-year anniversary, I drove a golf ball 275 yards. On the 3-year anniversary, I hit a baseball pitched by my son off the centerfield fence, then hoisted him in the air. That's joy, made possible by science.

"Close to four years later, I am still here, and not just here. Last weekend, I skated in my daughter's parent against kids hockey game. At the time of my diagnosis, I was worried she would

remember me only in photos. She was four; my son was seven. Today they are 8 and 11. Because of tofersen, I am here, alive, in every family memory, in every family photo.

"I continue to work full time and provide for my family as an assistant general manager of the National Hockey League team. Be clear. As I sit here, I am not dying. My legs and lungs remain completely healthy. I use no breathing support. When this call is complete, I will do what I do most afternoons, step outside, take in a deep breath of air, and go for a walk, alone, fast-paced, under my own power. While I do, I'll pray that you make what appears to be an obvious decision. My life depends upon it. The lives of my children, my sister, her children, my cousins and their children, stand to depend upon it. Our lives are in your hands. Thank you."

DR. MONTINE: Thank you.

Speaker 15, would you please begin by stating your name and any organization you are are representing, for the record?

MS. WEBB: Good afternoon. My name is Lauren Webb, and I'm the chief advocacy and outreach officer for the Les Turner ALS Foundation. My only disclosure is that we receive less than 5 percent of our annual funding from pharmaceutical companies, including Biogen.

Thank you for the opportunity to speak today. Our foundation has been closely associated with SOD1 ALS for many years; in fact, SOD1 was co-discovered at the Les Turner ALS Center at Northwestern Medicine, and the center was the site for both the phase 3 VALOR trial and of tofersen and the open-label extension.

We understand the science behind SOD1 ALS and are encouraged by the results that suggest an early start and extended use of tofersen may help stabilize muscle strength, respiratory function, and quality of life. And with more than 45 years of experience supporting people with this and all forms of ALS, we understand the urgency and the need for treatment.

Our support service coordinators work with

families who have lost loved ones across multiple generations to SOD1 ALS. From firsthand experience, we can testify to the emotional trauma for these families is overwhelming. We have worked with people who have lost both their spouse and a child to the disease. We have provided a wheelchair to one woman, and a few years later provided the same to her brother.

Speaking personally for a moment, early in my career, I met a 35-year-old woman who had the A5V variant in the SOD1 gene. This is a very aggressive form of ALS that also affected her mother. I remember taking her 10-year-old daughter to get a snack while the genetic counselor explained the results to her parents. We sat in the hospital cafeteria, and I quizzed her on the state capital. That little girl lost her mother 9 months later.

People living with SOD1 ALS need more than support from us. They need a chance to believe in the share of their lives and their families. They need the cause to believe that the pain of this

terrible disease will be a different experience for their children. They need hope. Nothing can mean as much to these families as the first therapy to slow progression of the genetic form of ALS, and that's what tofersen does.

I think back on that cafeteria, and I want this story to unfold differently. I wanted to take that 10-year-old girl back upstairs to find her mother holding a copy of her SOD1 lab report and a prescription for tofersen. I wanted that mother to have a chance to see her daughter graduate. We believe that tofersen represents a significant enhancement to the treatment of SOD1 ALS. There is urgent and unmet need, and the evidence is compelling. We urge you to recommend approval. Thank you.

DR. MONTINE: Thank you.

Speaker 16, will you please begin by stating your name and any organization you are representing, for the record?

MR. OLSON: Hello. My name is Tucker Olson, and I come to you, the FDA, as a member of a family

affected by SOD1 ALS. Furthermore, I am speaking as an individual who inherited the SOD1 mutation from my deceased father. I have no financial disclosures.

My immediate family story dates to the time in which the SOD1 gene mutation was discovered to be causative of ALS, our family's SOD1 ALS variant, L145F, being one of the first SOD1 variants discovered. My grandmother developed ALS in the late 1980s. She succumbed to the disease in 1994, shortly before my fourth birthday. At that point in time, no treatments existed for the disease. Around the year 2000, my Uncle John was diagnosed with ALS. It was then that my family learned that we were affected by the ultimate [indiscernible] dominantly inherited form of the disease.

My uncle selflessly volunteered to participate in the clinical trial, knowing very well that he will likely not benefit from it but that his brothers and sisters, his children, nieces and nephews may one day benefit. He would later be abruptly pulled from the trial due to its

ineffectiveness. My Uncle John would succumb to ALS in 2005. He never had the opportunity to meet most of his grandchildren.

Three years after my uncle's passing, my father, Rick Olson, would be diagnosed. He to selflessly participated in a clinical trial in hopes that his family would one day benefit. After 5 years of surviving, my father succumbed to the disease in 2013. He would not have the opportunity to witness my younger sister and I graduate from college, nor will he ever witness us start our own families and have our own children one day. While grateful for the limited time he held with my older sister's children, his grandchildren, he would not be able to witness them grow into the remarkable people that they've become.

Four years after my father's passing, his youngest sister, my Aunt Patty, was diagnosed with familial ALS. This diagnosis would occur months after her neurologist disregarded her initial symptoms. I will address this diagnostic delay momentarily. At this time of my aunt's diagnosis,

there were no SOD1 clinical trials in which she was eligible for. My aunt succumbed to the disease just 10 months after being diagnosed, and passed in July of 2018. She would never get to see her daughter graduate from high school, nor would she be able to enjoy her son and daughter's adulthood years, as they've grown into some of the most kind-hearted and caring people I know. She would be proud.

Research in 2019 on 66 SOD1 ALS cases reported an average age of onset of 44 years old. The median diagnostic delay was 14 and a half months for all SOD1 mutant patients, with a maximum diagnostic delay of 36 and a half months. [Indiscernible] history, otherwise referred to as fALS patients, the median diagnostic delay was 20 months compared to the median of 8 months for those with no known family histories. This is not acceptable. Like mine and other SOD1 families you have and will continue to hear from today, my family and other SOD1 families deserve better.

As the data indicated, the sooner tofersen's

in bodies, the longer people live with increased functionality. I'm asking you, the FDA, to approve tofersen for the symptomatic and presymptomatic populations. Data from tofersen's open-label extension shows early treatment works much better. Tofersen has the possibility of giving my family something that we have not always had, the opportunity to experience life's milestones and the joys of watching our children grow. Please approve tofersen. Thank you.

DR. MONTINE: Thank you.

Speaker 17, will you please begin by stating your name and any organization you are representing, for the record?

MS. MORRIS: Hello. My name is Jessica Morris, and I am not representing anyone. I am a 35-year-old mom of three, who was diagnosed with ALS in September of 2022. I am part of the Payne family who has lost 22 family members to ALS due to our SOD1 mutation. We lost my father to ALS when I was 5 years old. In March of 2022, I started noticing I was having a more difficult time going

up the stairs. I begin testing in June 2022, and in September of that same year, my physician confirmed the ALS diagnosis I already knew I had.

On the drive to my first ALS clinic visit, all I could think about were the 10 short months my father lived following his diagnosis and how I would likely follow in his path, leaving my husband and our three children behind. He was 32 at diagnosis, and I was 34. It was difficult not to see the similarities between my father's journey with ALS and the journey I was about to embark on; however, one of the first things my physician said was, "This is not your Dad's ALS," and she was right. Now, in 2023, we are making progress in slowing and hopefully one day stopping this ugly disease.

I have been taking tofersen for several months, and I'm so grateful for the opportunity to have a chance at slowing my progression. It's not often an ALS patient has hope, and that's exactly what tofersen represents to me, hope. In the last month, I've had multiple family members comment on

small improvements in my walking. Just yesterday, I was able to walk in a bottom floor of my home without a cane, and I'm also noticing that while stairs are still hard, I'm able to walk to the second story of my home without crawling up the larger middle step as I had been doing 4 weeks prior. The only thing I can attribute these positive changes to is tofersen.

When I was diagnosed, I made a promise to my family that I would never give up fighting for more time with them. I will fight for years, months, weeks, days, hours, and even minutes just to be there for more goodnight kisses, more bedtime stories, to watch football games with them, gymnastic recitals, and to watch my children walk across that stage at graduation. Please help to approve tofersen so I keep fighting with every tool possible to keep my promise of more time with my family. Thank you.

DR. MONTINE: Thank you.

Speaker 18, will you please begin by stating your name and any organization you are

representing, for the record?

DR. MAYL: Good afternoon. This is Dr. Keith Mayl. I am a physician/scientist in neurology with expertise in neurodegenerative diseases. I have treated multiple patients with ALS, including those with rare genetic forms. I led the VALOR clinical trial and open-label extension, and the subsequent expanded access program at King's College Hospital. [Inaudible - audio gap] my ALS patients with tofersen and my interpretation of the data, and I would like to highlight that I have no financial relationship with Biogen.

The severity of ALS and the destructive effect it has on patients and their families is undeniable with random variables [indiscernible]. The genetics of populations of ALS are further burdened by the generational trauma of losing multiple loved ones, as we are currently hearing. The need for disease-modifying intervention is urgent and would give hope to all individuals and families affected by ALS.

While I acknowledge the trial did not meet its primary endpoint, the totality of the data from VALOR and the open-label extension clearly suggests a clinical benefit for patients treated with tofersen. Stabilization of the disease, as evidenced by the revised ALS data, is a remarkable achievement that comes after countless clinical trial failures over the last 20 years. Furthermore, a 27 percent increase in muscle strength in patients treated early with tofersen is totally unprecedented in ALS and inconsistent with the natural history of the disease.

These findings cannot be attributed to anything other than the disease-modifying effect of tofersen, which is strongly supported by the NfL data. The prognostic and predictive value of NfL in ALS are well recognized, and thus sustained reductions in NfL in patients treated with tofersen clearly reflect the biological effects.

I have witnessed firsthand the transformative effect of tofersen in 6 patients with SOD1 ALS. Beyond stabilizing their disease

progression, it has allowed them to maintain their independence, their ability to work full time, and their ability to enjoy a meaningful quality of life. The benefits of tofersen extend not only to patients treated with it, but also to the families of those affected by this dreadful disease.

These success stories are hard to capture in the data, but are the lived experiences of several patients treated with tofersen. I urge the committee to endorse NfL as a surrogate endpoint in SOD1 ALS, and to consider the totality of the data, which overall support a treatment effect. I also urge the committee to consider the unique challenges in rare disease clinical trials, including the disease heterogeneity with small numbers of patients and the ethical challenges of having longer placebo-controlled trials in such patient populations.

In my medical opinion, the risk-benefit profile favors treatment with tofersen for patients with SOD1 ALS. With that in mind, I appeal to the committee to vote in favor of full approval for

tofersen to ensure access for all patients with SOD1 ALS, as we can no longer tell our patients that there is nothing we can do. Thank you for your time today.

DR. MONTINE: Thank you.

Speaker 19, will you please begin by stating your name and any organization you are representing, for the record?

MS. ABREVAYA: "My name is Brian Wallach. I am testifying for myself and for all ALS patients. We do not have a financial relationship with the sponsor, and the powerful voice you hear is my wife, Sandra, as ALS has robbed me of my voice. We are also the co-founders of I AM ALS, which has no financial relationship to the sponsor. Please make sure to note this, as Caroline Renko, who testified in slot 11, just blatantly lied by suggesting that I AM ALS has any financial interest with the sponsor.

"I have three points today. First, all of the patients and family members who testified today are just human beings. That means the questions

you are being asked to consider are ones that are not academic, but rather they directly impact real people and families whose lives are literally in your hands. For many who spoke today, they have lived with the knowledge that SOD1 has taken the lives of their family members and may take their life if we do not act now.

"Second, you may be wondering why a person living without SOD1 ALS is testifying. I am here to make sure you know how important this ADCOM is to the the entire ALS community. Every step forward for some patients is a step forward for the whole community as we seek to transform ALS from fail to chronic. For 30 years, since we discovered SOD1, we have all watched SOD1 patients be diagnosed and die quickly. The need of SOD1 patients for a drug like tofersen, that has the ability to reduce NfL and slow down, or even stop, ALS is clear. SOD1 patients are more than willing to accept the risks of tofersen, which, by the way, are the same as any intrathecal injection.

"Finally, if you think you are protecting

SOD1 patients by denying accelerated approval, you are not. The way you protect them is to recommend approval under the accelerated approval pathway. Here, the sponsor has already proposed additional studies that will further confirm the predictive value of NfL. In addition, you have multiple sets of data that show that tofersen reduces the amount of SOD1 protein and the level of NfL in patients. This data is supported by an ever-increasing litany of publications that conclude that NfL is correlated with disease severity, disease progression rates, and survival in patients with ALS. The science shows that a reduction in NfL is reasonably likely to predict clinical benefit.

"In the SOD1 context, a drug that extends the lives of SOD1 patients like tofersen is absolutely unprecedented. SOD1 patients do not want to try anything, but they definitely want to try a safe and effective treatment."

MR. WALLACH: [Indiscernible].

MS. ABREVAYA: "There is only one right answer here."

MR. WALLACH: [Indiscernible].

MS. ABREVAYA: "I just hope you have the courage to recommend approval. Thank you."

DR. MONTINE: Thank you.

Speaker 20, please begin by stating your name and any organization you are representing, for the record.

MR. LEGG: My name is Todd Legg. I'm speaking on behalf of the Donald [ph] family. Thank you to the FDA advisory committee for listening to me today. I'm not being compensated in any way for speaking.

I'm sure you all know about ALS. My family found out about it, really, in 2009 when my mother was first diagnosed. She was the first in my family to be diagnosed, and she passed away in 2010. In August 12, 2020, I received my death sentence; however, there was a small light shining through the darkness of hell. Maybe I would carry the SOD1 gene which has a promising treatment called tofersen. Almost a month later, I was at the University of Pennsylvania getting into the

VALOR study, and in October I got my first lumbar puncture. Maybe it was going to be drug, maybe placebo, but I don't care. It was great because I was on the right track, and there was hope.

I was quickly declining. I was hoping to be able to finish my year out as a high school math teacher. At 47 years old, I wasn't sure if I was going to make it to see 50, but here I am. I was certain I was getting placebo because I kept going down, especially in breathing. Then in January and February, my SVC numbers started to hold, and have held fairly well since then. I believe I was getting drug the entire time. I mirror all of the graphs we saw today. It just took time for it to count in the years of the toxic protein, my gene producers.

My story, it is anecdotal evidence, but tofersen has allowed me to continue my life. I'm still teaching every day, still splitting firewood by hand, playing golf with my wife, and I get to coach my 9-year-old son's baseball [indiscernible] team. I know the decisions are based on data, so

here is some data I have gotten. My SVC scores in April of 2020 was 74 percent; 2021, 46; '22, 44; and just February of this year, 42.

I have changed nothing in that time frame other than tofersen, and it's helped me, and it's done what it's supposed to do. I've had 34 lumbar punctures and presumably 33 tofersen doses. I've had very little side effects and, in fact, most every day I'm back to work the next day. I'm certain that without tofersen I would not be here unless I was on full mechanical support.

I understand the probability of getting this gene, and passing along hell over my family is over 50 percent in each generation. It was 3 for 3 in my mother's generation and 5 for 7 in my generation. I have two sons that have not been tested; however, odds say one of them will carry the gene. The success of tofersen will not only help families with the SOD1 gene, but should also pave the way for investments in research for other gene therapy for ALS and other diseases. Please vote to recommend tofersen for full approval.

Thank you again.

DR. MONTINE: Thank you.

Speaker 21, would you please begin by stating your name and any organization you are representing, for the record?

MS. GASCOIGNE: Hi. My name is Sarah Gascoigne, and I'm representing myself, and I have no financial relations. I'm a member of the Payne family that was previously mentioned.

Growing up, I knew that my family always carried the disease called ALS. Today, as was mentioned, we've lost 22 family members. With a disease that was just hopeless, sad, and scary, it was not really talked about because there was nothing you could do about it, but tofersen has changed that conversation for our family.

My firsthand experience with ALS began in 2015 when my dad was diagnosed. Over a course of 3 years, we watched the strongest man we knew lose his ability to walk, talk, use of arms, and eventually breathe. There was nothing we could do. We said goodbye to him in 2018. My aunt was

diagnosed in January of 2020 and was denied access to the tofersen trial. We said goodbye to her just a short 2 and a half years later. Again, there was nothing we could do.

In August of 2020, at the age of 26, I was officially diagnosed with ALS. I was devastated, and I thought my life was going to be over. A family member told me about the promising tofersen trial. I contacted every site in the Midwest and was accepted into the trial. Finally, there was something we could do. I was diagnosed August 11th in 2020 and had my first trial injection a short 2 weeks later. In the 2 and a half years I've been in the trial, and now open label, I've had no changes in my functioning. I am the same today as I was the day I was diagnosed.

I'm going to put this in perspective for you. The average life expectancy of a person with SOD1 ALS is about 2 years and 8 months. Think about that. Without tofersen, I would likely not be here. Because of tofersen, I'm living a very normal life. I'm traveling, I'm going to work

every day, and I get to love being an aunt to my wonderful nephew. I'm living a very normal 29-year-old life. Because of tofersen, I look forward to my future. I don't fear my future. I know I'm lucky, but I also know that I am a walking, talking, living example that tofersen works, and why tofersen needs to be approved and made available for all SOD1 families.

My uncle was diagnosed in 2021, and thankfully, due to the EAP, has been able to receive tofersen, but we can't rely on the EAP for drug access. My family, along with all other SOD1 families, have had to say goodbye far too many times. Tofersen will change that. We need tofersen for our families that are living today with ALS, and for our cousins, brothers, sisters, and our children.

Tofersen has changed the outcome of SOD1 ALS. Tofersen will allow us to live. Today I'm asking you to hear us, and hear our stories, and recommend tofersen for FDA approval. Thank you for your time.

DR. MONTINE: Thank you.

Speaker 22, will you please begin by stating your name and any organization you are representing, for the record?

MS. BALAS: Good afternoon. My name is Calaneet Balas, and I am the president and CEO of the ALS Association. I have no personal conflicts to disclose.

The ALS Association is the largest philanthropic funder of ALS research in the world. Our goal is to make ALS livable for everyone everywhere until we can cure it. This meeting is a step forward toward that goal, as the committee considers the application for tofersen, for the treatment of ALS associated with mutation of the SOD1 gene, a particularly rare and aggressive form of an already rare and devastating disease.

The ALS Association only makes recommendations on drug approvals after independent peer review process. Based on this analysis, we believe tofersen meets all the conditions required for accelerated approval. First, tofersen is

intended to treat a serious condition. People with most common SOD1 mutations develop this disease at a younger age, and on average live for less than 2 years after being diagnosed. Second, tofersen demonstrates an effect on the surrogate marker that is reasonably likely to predict clinical benefit, the marker, NfL, which you've already heard much about today.

While the phase 3 VALOR trial did not meet its predetermined primary endpoint, tofersen did reduce NfL levels in the blood by 50 percent within 12-to-16 weeks. These results suggest that the 28 weeks allotted for the initial blinded phase of the trial were not long enough to demonstrate clinical benefit, but long enough to show biological effects. These effects did translate into clinical benefit during the open-label extension.

Early indication of tofersen significantly slowed the decline of clinical function by an average of 3 and a half points. Tofersen also significantly reduced decline in respiratory

function, muscle strength, and quality of life. To our knowledge, this is the first drug to have the effects on these measures.

I recognize that this committee and the FDA have a tough decision to make since the VALOR trial did not meet its primary endpoint; however, drugs granted accelerated approval are often required to confirm anticipated clinical benefits through postmarketing trials. It would not be ethically or operationally possible to run a new larger or longer randomized trial since SOD1-linked ALS impacts about 2 percent of the people diagnosed with ALS, and therefore it's extremely rare. Fortunately, the ongoing ATLAS phase 3 prevention trial could serve this purpose.

For all these reasons, I respectfully request you make a favorable recommendation to the FDA supporting approval of tofersen. People with SOD1-linked ALS and their healthcare providers should have full access to this drug as soon as possible. Our community cannot wait. Thank you.

DR. MONTINE: Thank you.

Speaker 23, will you please begin by stating your name and any organization you are representing, for the record?

DR. GUPTA: Good afternoon. My name is Ravi Gupta, and I am a primary care physician and health policy researcher who examines FDA regulatory processes. I'm speaking today strictly on behalf Doctors for America, which is an independent organization of more than 27,000 physicians and trainees from across the country, addressing access to affordable care, community health and prevention, and health, justice, and equity. Doctors for America focus solely on what is best for our patients, not on the business side of medicine, and does not accept any funding from pharmaceutical or medical device companies.

As part of Doctors for America, the FDA task force is dedicated to ensuring that therapies approved for use are proven to be clinically beneficial before prescribed. As a primary care physician, I care regularly for patients who are afflicted by devastating illnesses without existing

treatment like ALS.

Moments when I have to tell my patients that there is, unfortunately, no cure to their ailment are among the most difficult of my profession, and on behalf of Doctors for America, I want to acknowledge the very real challenges for patients living with ALS. There is a deep need for treatments for this disease. In that vein, we want to be sure that therapies that come to market do in fact work for patients suffering from ALS.

Doctors for America is concerned about drug approval for tofersen, given that the drug did not meet clinical endpoint in the phase 3 pivotal trial, nor is the surrogate endpoint of neurofilament light concentration validated. However, Biogen, the manufacturer of tofersen, is seeking accelerated approval, based on this unvalidated surrogate endpoint and without additional confirmatory evidence of clinical benefit.

Ultimately, it is of vital importance that we uphold the integrity and consistency of the FDA

regulatory system and the evidentiary standards upon which it is based, and to do so, the FDA must require convincing evidence that a drug approved, including for the accelerated approval pathway based on a surrogate marker, is effective in the patients that it claims to help. And we say this with a clear-eyed recognition that patients with ALS, and their loved ones, suffer deeply from this catastrophic illness.

As doctors, we weigh the benefit and consequences of treatments, and discuss them with our patients every day. We do not believe that patients should be prescribed drugs without proving meaningful clinical benefit. We want nothing more than an approved treatment for ALS, but we ask respectfully that there be a demonstration of effectiveness. Thank you for the opportunity to offer comments.

DR. MONTINE: Thank you.

Speaker 24, will you please begin by stating your name and any organization you are representing, for the record?

MR. MATHEW: Hello. My name is Reuben Mathew. I'm representing myself. Thank you to the committee for giving me this platform.

I'm a fourth-year medical student, soon to become a combined medicine and pediatric resident. One of the core tenets of medicine that we're taught is to treat patients, not the numbers. That is the heart of the issue with this medication. ALS is a horrific disease. I've had an elderly patient recently diagnosed with ALS, and I know how much his family wanted any relief for him.

Patients deserve the best we can offer. It is my opinion that Biogen's tofersen does not represent this best. The method of administration for this medication is invasive and not without significant risk. The results may be promising but require further study to validate the direct relevance of neurofilaments to ALS to generate actionable evidence on the effects of tofersen on the primary endpoints of ALS patient function. We do not need more medication to the marketplace that have unproven benefits. Such multiplicity of

options muddies the waters for clinicians and patients.

The evidence of the surrogate clinical markers and the studies to date are not strong enough at this point to overwhelm the abundance of caution we must take with patients as vulnerable as these ALS patients. I'm here to ask the FDA to uphold the strong standard of evidence of clinical efficacy on the products they approve. Thank you.

DR. MONTINE: Thank you.

Speaker 25, will you please begin by stating your name and any organization you are representing, for the record?

MS. GRANNING: Hi. I'm Julie Granning. I am representing myself, and I'm not receiving compensation.

"Lost time is never found again." I lost my mom, Patty, to SOD1 ALS in January 2014. Her decline was fast, too fast, just 18 months from diagnosis to death. To ALS patients and their families, time is the most important thing; quality time even more so. If my mother had more time,

even months, she would have been there for some of my biggest life milestones.

Here is my wedding, the September before her death. She was on a ventilator and could not leave hospice. I got married without my mom. At least she had her own party, where she watched a recording of my ceremony on a laptop screen. Two months less decline would have had her at my wedding.

We spread her ashes in the spring, just 4 months after her death. I woke up that morning nauseated and realizing that very day, I was, in fact, pregnant. Four months more time, and I could have told her the happy news; instead, I told the tree as I spread her ashes. I went through my pregnancy and birth without my mother. I had my first baby just 4 days before the first anniversary of her death. Just one more year, and she could have been a grandmother. She would have loved being a grandmother.

We cannot go back in time and give my mother more, but you can give me more time. I inherited

the SOD1 gene, a variant that wasn't eligible for the ATLAS trial. Currently, I am, like so many others, at the mercy of a clinician's diagnosis, and the EAP, and you, the FDA. What could treatment, and therefore time, do for me if tofersen becomes available? I'm 38 years old, and I have two boys, age 5 and 8. The average age of onset is 45. Forty-five. What time will I get with my boys?

How many more tee-ball games will I coach? Will I still coach when they start baseball? Will I see my boys learn to drive and get their licenses? Will I see them graduate high school, college, find their careers? Will I see them fall in love, get married? Will I meet my own grandkids? Will my kids be here with you in 30 years begging for their lives? Please approve tofersen. Please give me time. Please give them time. Let me live my life, and let them live their lives. Thank you.

DR. MONTINE: Thank you.

Speaker 26, will you please begin by stating

your name and any organization you represent, for the record?

MS. LORENZ: Hi. My name is Michelle Lorenz, and I am with Voices for ALS. Neither I nor our nonprofit has ever received any money from pharma, and we have no conflicts of interest.

A mother buried her sons, both of them, at 29 and 30 years old. Today we honor John and Ethan. She wanted to speak today, but her pain is too raw. Our friend, Mayuri, was diagnosed at 32, with a rare variant, but without a family history her genetic testing was delayed. Thus, when she found out she was a carrier of the SOD1 mutation, she didn't qualify for the tofersen trial, nor the tofersen EAP.

In contrast to the reports from Dr. Miller you heard earlier today, let me be clear. Mayuri's score on the ALSFRS-R is a 1. Her brother, too, wanted to speak today, but his anger is too real, so I'm speaking for them. Friend after friend, and family after family have been devastated. Survivors are afraid of the next muscle twitch,

afraid to have children, and yet afraid to get tested, as there's been no hope, but today you have the power to rewrite their families histories, just as tofersen has rewritten the stories of so many in the VALOR trial.

Today I'm speaking in support of the accelerated approval of tofersen. To that end, I have three points to discuss. First, patient-reported outcomes and real-world evidence are evidence. No one knows better how a drug makes them feel and function. No one knows more about a clinically meaningful impact than the patients themselves. Believe them. Patient-reported outcomes aren't anecdotes, as some have said. They are legally admissible evidence.

In the 21st Century Cures Act, Congress encouraged the FDA to consider real-world evidence and patient experiences, and in its 2019 guidance document, the FDA agreed that patient-reported outcomes can be used as evidence in support of efficacy. Commissioner Califf himself, just a few months ago speaking at NORD, said patient

experiences can support and strengthen the empirical evidence. Thus, the patient-reported outcomes you heard today are part of the totality of the evidence that proves tofersen is reasonably likely to have a clinically meaningful impact.

In the written comments and in today's heartbreaking testimony, the patients on tofersen told you how it changed their progression, halted their progression, and improved their quality of life. Dr. Miller shared 4 case studies. People reported less falls, more strength, and the ability to push themselves out of chairs. Another person can pour a full gallon of water with his right arm. To be clear, for those of you not familiar with the ALSFRS-R, it would not capture a single one of these changes. When people are dying, they know when a drug helps them live.

Second, the FDA can use the accelerated approval pathway to ensure humanity and concurrently advance the science with a phase 4 study, including a patient registry and biorepository. Because tofersen is delivered via

lumbar puncture, it presents a unique opportunity to collect CSF biomarker data to advance the science, not just of neurofilament light, but of all the important CSF biomarkers. Equally important, a patient registry and biorepository would allow the gathering of data from the underrepresented minority groups, many of whom don't participate in clinical trials.

Finally, your question you have to answer today is one of risk-benefit. We're grateful that the FDA has acknowledged that people with ALS are willing to accept more risk, as nothing is as horrific as the suffering caused by ALS. But I'm also asking you to consider the risk of a type 2 statistical error, the irreparable harm of delaying --

DR. MONTINE: Excuse me.

MS. LORENZ: -- or denying approval of a drug.

Just one more sentence.

DR. MONTINE: Please wrap up. You're far over.

MS. LORENZ: Thank you.

The FDA has no guidance on type 2 errors, but in a 100 percent fatal disease, the most common A5V variant killing in 1.2 years, people don't have time to wait. As Sandy Morris has often said, "The ALS clock waits for no one."

DR. MONTINE: Thank you, Speaker 26, and that concludes the open public hearing portion of our meeting. We will no longer take comments from the audience.

We're now going to take a 15-minute break. Panel members, please remember that there should be no chatting or discussion of the meeting topic with anyone during the break. We will resume at 3:52; 3:52, please. We're at break.

(Whereupon, at 3:37 p.m., a recess was taken.)

DR. MONTINE: Welcome back. I want to thank, again, everyone who contributed to the public session for your poignant and meaningful contributions.

Jessica, I just want to check you can hear

me. Will the slides change back?

DR. SEO: Yes, Dr. Montine. We can hear you, and the slides will change momentarily.

Clarifying Questions (continued)

DR. MONTINE: Great. Thanks.

Before we move to discussion, there were two panel members, Dr. Alexander and Dr. Apostolova, who had additional questions for the Biogen team when we ran out of time earlier, so we'd like to return to those two panel members so that they can ask their question, each can ask their question, before we move to the discussion session.

Dr. Alexander, would you, please?

DR. ALEXANDER: Yes. Thanks, Dr. Montine. It's Robert Alexander.

I wanted to ask the Biogen team another safety question around the risk of myelitis and other serious AES, and if they have an understanding if the risk is continuous. In other words, as long as patients are receiving treatment, does the risk exist or is it limited to some initial period after dosing is initiated, or is

there any concern that the risk might actually be increasing over time with repeated dosing? Thank you.

DR. FRADETTE: This is Stephanie Fradette for Biogen, and I'll ask Dr. Fanning to comment.

DR. FANNING: Yes. This is Laura Fanning from Biogen. Basically, there is not a clear association with timing. The range of doses of tofersen received prior to onset of one of these events was anywhere from the first dose up through more than 20 doses. The majority of them happened within approximately the first 5-to-10 doses; however, there does not appear to be a very clear association for a specific time point. On the other hand, there also does not appear to be a dramatically increased risk over time. This doesn't seem to be getting more frequent with a longer duration of exposure.

I realize that's not an entirely clear answer, but on the other hand, the absolute number of cases is not particularly large, so I expect that we will understand this better as we gain more

experience with this drug, and we continue to monitor. Thank you.

DR. MONTINE: Thank you.

Dr. Apostolova, please.

DR. SEO: Dr. Montine, this is Jessica. It looks like Dr. Apostolova is connecting her audio. Let's just give it a moment for her to get connected.

DR. MONTINE: Okay.

(Pause.)

DR. APOSTOLOVA: Hello?

DR. MONTINE: Hello. Please go ahead.

DR. APOSTOLOVA: Yes. Can you repeat your question? I was trying to connect.

DR. MONTINE: Oh, excuse me. Earlier you signaled that you had a follow-up question for the Biogen team, so we just wanted to take a few moments to allow you to ask that question.

DR. APOSTOLOVA: Yes. It was about the side effects, and which side effects caused patients to discontinue, or patients were challenged later, and that was answered during the Biogen

presentations --

DR. MONTINE: Okay. Well, thank you very much.

DR. APOSTOLOVA: -- or doing the FDA presentations.

Questions to the Committee and Discussion

DR. MONTINE: Okay.

The committee will now turn its attention to address the task at hand, the careful consideration of the data before the committee, as well as the public comments. We will proceed with the questions to the committee and panel discussions. I would like to remind the 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 questions or comments concerning its wording, then we will open the question to discussion.

Question 1 discussion is here. Discuss whether the available evidence supports that a reduction in plasma neurofilament light

concentration observed in tofersen-treated patients with amyotrophic lateral sclerosis, secondary to a mutation in SOD1 ALS, is reasonably likely to predict clinical benefit for these patients.

Are there any questions from the panel concerning this discussion point; how it's worded, I mean?

(No response.)

DR. MONTINE: If there are no questions or comments concerning the wording, we will now open this to discussion.

Let's see. Dr. Alexander, I believe you had your hand up first. Would you please begin?

DR. ALEXANDER: Thanks, Dr. Montine. It's Robert Alexander. I don't know if it's directly related to this question but as a consequence of this question. This is really directed for Dr. Buracchio and the FDA team.

I'm wondering how they're going to confirm how one will be able to confirm clinical benefit, assuming an accelerated approval, because the ATLAS trial, looking at presymptomatic subjects and an

effect on presymptomatic, it doesn't necessarily imply efficacy in symptomatic subjects, and it's not clear to me what else is going to be learned from the continuation of the open-label extension.

It's important in understanding the consequence of accelerated approval and whether they're really going to be able to verify the clinical benefit once the drug is available through accelerated approval. Thanks.

DR. MONTINE: Dr. Buracchio, are you there?

DR. BURACCHIO: Okay. Can you hear me now?

DR. MONTINE: Yes, I can.

DR. BURACCHIO: Okay. Sorry.

I would start my saying you've got two different pieces of evidence here that you're considering. For the first piece, which is the ATLAS study, even though the patients are presymptomatic, we do still consider that to be within the spectrum of the disease for SOD1 ALS. So we do consider that even though it's an earlier stage of the disease, that a benefit in that population could be considered to support a benefit

in the symptomatic population as well. Especially looking at and seeing clinical trends already in the symptomatic population, then I do think that a clear signal in the presymptomatic population could serve as confirmatory evidence of a potential benefit in the symptomatic population.

Regarding the other piece, which would be the continuation of the open-label extension, that could be a little more tricky. I think we do know that there are issues or concerns with bias with using an external control; however, it could be considered that when we look at external controls, we want to be able to say is the natural history of the disease well defined; is the treatment effect large and able to overcome the biases of an external control; and is there a hard endpoint.

So I think of the things that have been presented, survival is clearly a hard endpoint. If we were able to have a well-defined natural history of survival in a natural history population -- and it sounds like the A5V population has probably got one of the best characterized survival rates. If

we saw a clear benefit in survival that was outside of the norms of what would be expected to be seen in the natural history of the disease, that could potentially be supportive.

We're also hearing about potential improvements in strength, and if that's really not ever seen in the disease, or rarely seen in that disease, and defined well in a natural history study, that could also be something that we could consider. It is a little hard to prospectively say that the open-label extension will be able to provide confirmatory evidence, but I think we're open to seeing whatever data they could provide from that study that might provide confirmation.

DR. MONTINE: Thank you.

Dr. Romero, you also have raised your hand.

(No response.)

DR. MONTINE: Dr. Romero, I can't hear you.

(No response.)

DR. MONTINE: Well, perhaps we'll cycle back.

Dr. Simuni, you have raised your hand.

DR. SIMUNI: Hi. This is Tanya Simuni, Northwestern University. As advice and in order for us to address the question at hand, first of all, I want to highlight for us, as it's stated on the screen, that we are adjudicating not on the validated biomarker. We are adjudicating on reasonably likely to predict clinical benefit.

From my review of all the data pre-meeting and the data presented during the meeting, we're addressing three key points: mechanistic evidence, and the data unequivocally provided that based on the tofersen mechanism. It impacts the SOD protein. The next one is downstream effect on the neurodegenerative biomarker, i.e., NfL, and again, the data presented unequivocally demonstrates reduction of the biomarker.

The next point in discussion is prognostic value of NfL, and again, that's where I very much appreciate a very clear summary from the Division of Clinical Pharmacology from FDA, summarizing literature-based meta-analysis and the analysis from the 101C study. Constellation of that

evidence makes me adjudicate that there is sufficient evidence on combination of the literature in the study; that, yes, it does have the prognostic value.

The last question is obviously the most difficult one. The VALOR study did not meet its prespecified clinical endpoint, so it did not demonstrate efficacy. However, we are adjudicating on the entirety of the data, and the data from the open-label extension, mechanistic data, pointing to the time-based relationship between the effect on the protein as the biomarker of target engagement, followed by NfL as the reasonably likely biomarker, framed for the clinical separation, supporting it moving in the right direction.

All of these data make me make the conclusion that we have sufficient data to advise that it is reasonably likely. I very much recognize the separation of the opinion from the Division of Biostatistical team of FDA and the clinical pharmacology, but I think that the way we were hearing the data and the way we're asked to

adjudicate, we're adjudicating on the entirety of the data in a very rare disease, where another placebo-controlled study is not feasible. We need to question whether that's ethical or not, where there is a plan for the support of data as was summarized, so I don't need to summarize that.

So my conclusion is that, yes, we do have sufficient entirety of the data to conclude that there is reasonably likelihood of NfL being the predicting clinical benefit, and as such, supporting accelerated approval.

DR. MONTINE: Thank you, Tanya; very clearly laid out reasoning and conclusion, and I agree with Dr. Simuni's conclusion.

I would ask, as I call on subsequent panel members, if you feel comfortable, would you please comment on whether you agree or disagree with what Tanya just went through, the summary that she laid out for us?

In the order, Dr. Romero, you're next.

DR. ROMERO: Hopefully you can hear me now.

DR. MONTINE: Yes, I can.

DR. ROMERO: Great.

Yes, I agree with Dr. Simuni's assessment because the key of the question on the screen hinges on the reasonably likely components of the wording of the question. The question is not about a fully validated surrogate; the question is about a reasonably likely surrogate marker.

As such, the totality of evidence, even with the caveat of when the analyses were performed and the nature of the analyses, we should always balance the epistemic need versus the ethical considerations, and the epistemic needs should never trump the ethical considerations.

With the evidence that we have in maximizing the utility of every precious data point in a rare disease, there is reasonable evidence of the reasonably likely nature of NfL as a marker of clinical benefit. Thank you.

DR. MONTINE: Thank you.

Next is Dr. Weisman, please.

DR. WEISMAN: Yes. Dave Weisman, and I agree with everything that's been said, and I have

a bit of a question maybe for Dr. Miller.

We have SOD1 aggregates that are targeted and reduced. That's upstream. We have downstream NfL leaks that are also diminished. It appears, based on everything I've read about this, that this is almost monolithically tied to cell death, mechanically. Is there any reasonable data that contradicts that?

DR. FRADETTE: Dr. Miller?

DR. MILLER: I guess the short answer to that is no, I don't think there's any data that contradicts the idea that SOD1 mutations are causing death of the motor neurons. The death of motor neurons is leading to leaking out of neurofilament, or maybe sick neurons also leaking out the neurofilament, and that that process is slowing down blocking SOD1, and then reverses that whole pathway.

I think that's what you're asking, but, yes, it is, in a way, a clear link in terms of the way that I interpret the science. Does that answer your question?

DR. WEISMAN: It does, which the odds are very low that a clinical benefit would not follow, so, thank you. That clears it up.

DR. MILLER: I agree. Thank you.

DR. MONTINE: Thank you.

Dr. Mielke?

DR. MIELKE: Yes. Thank you. Michelle Mielke from Wake Forest. I completely agree with the previous responses in terms of the questions and thoughtfulness of the responses.

To add on to that, I want to even further highlight that there is in the literature strong associations between neurodegenerative diseases that are progressive in increasing NfL in both plasma and CSF, and also strong evidence that increasing NfL is associated with decreasing clinical function across neurodegenerative diseases, whether it's cognitive, physical function, or motor function.

NfL also increases with age, so the fact here that we're seeing that tofersen is associated with decreasing NfL, although late period as we

would expect, I think strongly suggests and supports the drug effects on NfL, and the fact that it is likely to predict a clinical benefit. Thank you.

DR. MONTINE: Thank you.

Dr. Kryscio, please.

DR. KRYSCIO: Okay. Thank you, Tom. It's Dick Kryscio, University of Kentucky. I just want to clarify the breadth of this statement. We've been hearing about the mITT population, the non-mITT population, and then I guess the joint, which is the ITT population. So this approval would apply to the ITT population; is that correct?

The second part of my question is, it would not necessarily be approved for any ALS patient who is not SOD1. Can anyone answer that?

DR. MONTINE: Perhaps, Dr. Buracchio, are you with us?

DR. BURACCHIO: Yes. Sorry. I had to unmute again. Yes, so I can address this.

First, the question about which population, in this situation we have asked you to consider all

the available data, so that would refer to the entire population, not just the prespecified mITT population from Study 101C. We would want you to consider all available data from the entire population.

Then as far as what population this would be indicated for, I think the applicant is seeking an indication specifically for ALS due to an associated mutation in the SOD1 gene. I can't speak to exactly what the indication statement would ultimately read, but, in general, I think we would have something along those lines where we would be specifying the genetic mutation since that is what was studied.

DR. KRYSCIO: Well, yes, that's what I'm hearing from, say, Dr. Mielke, is that many neurodegenerative diseases have increased NfL levels, neurofilament levels. So I just want to clarify that this is just for SOD1s, which is, incidentally, a very small proportion of the cases.

DR. BURACCHIO: Yes. In this situation, we are considering the NfL. It would be as a

surrogate marker in this specific population of the ALS SOD1 population and in the setting of this therapy specifically. So that if there was, theoretically, another therapy that came along targeting SOD1 mutation in ALS, we would look at that program separately on a case-by-case basis, and also the same for any other general ALS that was not specific to the SOD1 mutation.

DR. BURACCHIO: Well, thank you for answering the question.

DR. BURACCHIO: You're welcome.

DR. MONTINE: Thank you, Dick.

I think I'll just take a moment to summarize where I think we are, and then ask if there are any additional comments or questions.

So, in part, I'm reiterating what Tanya just went through, but think we have agreement that treatment appears to show target engagement through reduction in CSF SOD1. Treatment shows a reduction in plasma NfL concentration, which is best interpreted as a decreased injury to neurons.

I think all groups have agreed that the

trial did not meet any of its prespecified endpoints, and we haven't talked much in this part, but we will next. I believe there's agreement that the treatment does cause neurological serious adverse events that have been reviewed multiple times.

In addition to that, I believe we at least have consensus among the panel around this discussion point, and that, again, it appears we have consensus that in this context, SOD1 ALS, that the reduction in plasma neurofilament light concentration is reasonably likely to predict clinical benefit for this rare set of patients.

I put it in those terms, and I'm deliberately trying to provoke a discussion. If there are members of the panel who don't agree with that, it'd be great to hear from you now so we can fully discuss the issue before voting.

Dr. Gold, you've raised your hand.

DR. GOLD: Yes. Thank you. My sense is that there's, obviously, an unequivocal demonstration of target engagement. There is what

we would call a good strong pharmacodynamic signal in the reduction in NfL, and it kind of falls on the same question. It's not a rapid -- or at least part of what dogged the study is that there was a lag between the drop in SOD1 and what is, we believe, to be a related effect on NfL.

So I think my question is more along the lines of do we want to require, or would one need a certain minimum level of plasma NfL at baseline to be treated with this drug -- because my understanding is that the response was driven by the plasma NfL -- and B, what would we think in terms of the kind of communication to patients in the sense of it's going to take at least X amount of time before we start seeing it? If we're getting to the point we think that this is a biomarker or surrogate that is reasonably likely to bring clinical benefit, is this going to be a biomarker that is going to have to be followed over time? I think those are kind of related to this kind of question; that we're asking about the reasonableness of this to predict clinical benefit.

I'm sorry. I hope it's not precluding the discussion of some of the other questions, but as I was listening to the discussion, these questions were coming to mind. Thank you.

DR. MONTINE: Thank you.

Other panel members that would like to respond to the issues raised by Dr. Gold?

DR. MIELKE: Yes. This is Michelle Mielke from Forest, a couple things.

First, I appreciate Dr. Kryscio's question, and I didn't define myself enough. So it's not just the drop in the NfL, but I think it's particularly important, as was highlighted by the pharmacometric presentations, which were very clear, that it is clear that the NfL is likely related to the SOD1 ALS mutation, so certainly this wouldn't be for all neurodegenerative disorders, and likely for only those ALS patients that have this mutation.

Dr. Gold, I think your questions are great ones, not that we can necessarily answer many of these at this time. My assumption right now would

be that, yes, we would probably have to follow individuals longitudinally with NfL, but I don't know if there's a specific cutpoint at this time that could be determined. Of course, perhaps the sponsor has a response to that.

DR. FRADETTE: This is Stephanie Fradette from Biogen. We do not envision a scenario in which neurofilament levels would be informative as to whether or not treatment should be initiated or continued, et cetera. Of course, we understand that many clinicians may choose to follow neurofilament over time, but given the clinical effects that we're observing, you could also evaluate whether or not to continue treatment is appropriate in light of clinical response over time as well.

But I'd ask Dr. Miller to comment and share his perspective, as he's dealing with us at this moment.

DR. MILLER: Hi. Tim Miller, Washington University. In terms of following neurofilament, I think that many of us in clinical practice would

indeed be using neurofilament, that we'd be using that to help guide. And I think I predict that it will become part of practice, but it's going to depend on each of the physicians. I think we'd want to leave it up to each of the physicians.

I just want to comment on the level of neurofilament that was raised in that we've encountered some people with SOD1 ALS, for example, that have a slowly progressive form, maybe on the 10-year time course. From the data you've heard today, you would anticipate that that would mean that they have lower levels of neurofilament, and that's true for some of those people.

At least, one, these are early days to understand this, but someone who's getting tofersen in the expanded access program, who believes that there's a clinical response and the clinician believes that there's a response, started out with a very low neurofilament level. So I wouldn't want to tie necessarily to say people could respond; especially if they start with a very low neurofilament, I think we'd tie that clinically.

Thank you.

DR. MONTINE: Thank you.

Dr. Romero, please.

DR. ROMERO: Thank you.

I want to make sure that we separate three things. One is the question of potential use of NfL in clinical practice versus the use of NfL for drug development, and then the use of cutoff points. The conversation about NfL use in clinical practice I think is out of scope for this conversation.

The question about the use of NfL for drug development I think relates to several different things. There are, and we hope that this continues, other development programs for ALS, and if a sponsor chooses to use the entire distribution of baseline NfL to inform, for example, prior enrichment, I would say that's perfectly ok on the face of it. Of course, that needs to be put in a context with the individual product and the kind of design that is being thought about, but I wouldn't necessarily conclude that that should be the thing

to do in every case, based on the information that we have at this point.

Then the other piece is that of cutoff points. For drug development and the use of NfL at baseline, for example, trend enrichment doesn't necessarily require the definition of one-size-fits-all cutoff points. As long as you continue to extract valuable information from every precious data point, you could model the contribution of baseline NfL as a continuous covariate at baseline on the dynamic of NfL longitudinal dynamics and the relationship with clinical benefits; and that way, you could define trial specific enrichment targets, but that could not be interpreted as a one-size-fits-all cutoff point. I'd like to stop with that. Thank you.

DR. MONTINE: Thank you.

Dr. Apostolova, you're next, please.

DR. APOSTOLOVA: Yes. Great, and I'm following the comments of Dr. Romero. I really like this assessment.

In our pre-meeting materials, there were

some materials provided about the ATLAS study, which is the ongoing, double-blind, placebo control of presymptomatic carriers of SOD1, and it seems to indicate that an increase in NfL level to a prespecified threshold would be a requirement to initiate treatment.

I know that this is not the topic of today's meeting, but what is that prespecified threshold, and how is that determined for that study? And would that be in anyways leverage to the accelerated approval or in the future to how potentially full approval might develop? Thank you.

DR. FRADETTE: This is Stephanie Fradette from Biogen. Slide up, please, if we're able to.

Would be able to share the screen on the Biogen slide? Thank you.

Dr. Romero made an important distinction between the clinical trial setting and the real-world practice, but the question about the threshold established for the ATLAS study, as illustrated on this slide, we're monitoring

neurofilament levels on a routine basis in asymptomatic individuals, with a specific subset of rapidly progressive, highly penetrant SOD1, and we're waiting to observe a change in their neurofilament levels. We're looking for a level that is above 44 picograms per mL and has increased by at least 10 picograms per mL since the baseline of the study.

This threshold was informed based on data from participants in the pre-fALS study, so we looked at the totality of data both in those that experienced phenoconversion, as well as those that remained clinically asymptomatic, and used it to inform the time point or the threshold at which we were confident that we would observe clinically manifest ALS in the near future in the absence of an effective treatment. Slide up.

The slide that Dr. Miller presented earlier today, which reflects data from Dr. Benatar and the team at University of Miami, illustrates essentially the data underlying that threshold. So we took all of the samples from the pre-fALS study,

we ran them on the Siemens assay, which is what we've been using, and built a threshold trajectory model to inform the selection of that threshold.

It is important to note that that is specific to the ATLAS study, and that we will learn a great deal from that study as to whether or not that is the appropriate threshold, and what that threshold looks like across different matrices, analytes, and assays going forward. Thank you.

DR. MONTINE: Thank you.

I wish to thank everyone on the panel, and that's been a full discussion. Are there any other comments that a panel member wishes to make about this discussion point for question 1?

DR. WEISMAN: I have a brief question. Do any other drugs in ALS reduce NfL?

DR. BURACCHIO: Hi. This is Teresa --

DR. FRADETTE: This is Stephanie Fradette from Biogen. Oh, sorry.

DR. BURACCHIO: Go ahead.

DR. FRADETTE: Sorry, Dr. Buracchio. I apologize.

(Crosstalk.)

DR. BURACCHIO: I will just add --

DR. FRADETTE: I was going to -- go ahead

DR. BURACCHIO: Yes. I was going to say that I'm not aware of others that have been shown to lower NfL; however, I will say that NfL has only really recently made its way into clinical trials in the last few years, so there may be data coming on that, that we haven't seen yet.

Stephanie, feel free to add something more if you would like.

DR. FRADETTE: I completely agree. I think it's early days, and there are some early data coming out from from programs, as this is being monitored more broadly, and it'll be quite informative to look at those data in more detail. Thank you.

DR. WEISMAN: Thank you.

DR. MONTINE: Thank you. Thank you both.

Any further questions or comments on this point?

(No response.)

DR. MONTINE: Okay. Then we will proceed. If there is no further discussion on this discussion question, we will now move on to question number 2, which is a voting question.

Dr. Jessica Seo will provide the instructions for voting.

DR. SEO: Thank you, Dr. Montine.

Questions 2 and 4 are voting questions. 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; then 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.

Are there any questions about the voting process before we begin?

(No response.)

DR. SEO: I don't see any hands raised, so Dr. Montine?

DR. MONTINE: Thank you.

Question 2 for voting. Is the available evidence sufficient to conclude that a reduction in

plasma neurofilament light chain concentration in tofersen-treated patients is reasonably likely to predict clinical benefit of tofersen for treatment of patients with SOD1 ALS?

Do any panel members have a question about the wording of this question?

(No response.)

DR. MONTINE: If there are no questions or comments concerning the wording of the question, we will now begin the 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 result into the record.

(Pause.)

DR. SEO: Voting has closed and is now complete. The vote results are displayed, and I will read the vote totals into the record. The chairperson will go down the list, and each voting

member will state their name and their vote into the record. You can also state the reason why you voted as you did, if you want to.

There were 9 yeses, zero noes, and zero abstentions.

Dr. Montine?

DR. MONTINE: Thank you, Dr. Seo.

We will now go down the list and have everyone who voted state their name and vote into the record. You may also provide justification for your vote, if you wish to.

We will start with Dr. Weisman.

DR. WEISMAN: This is David Weisman, and I voted yes for all the reasons we discussed. It appears that NfL is bad for neurons and is tied with neuronal death, so if it's lower, then neuronal death should be lower. Thank you.

DR. MONTINE: Thank you.

Dr. Romero?

(No response.)

DR. MONTINE: Dr. Romero, you may be muted.

DR. ROMERO: Apologies. Can you hear me

now?

DR. MONTINE: I can.

DR. ROMERO: Okay. Great.

Yes. Again, the issue of the question was around the reasonably likelihood of NfL as a reasonably likely surrogate, and my vote is that the totality of evidence presented is a yes. Thank you.

DR. MONTINE: Thank you.

Dr. Apostolova?

DR. APOSTOLOVA: Can you hear me?

DR. MONTINE: I can.

DR. APOSTOLOVA: Oh, good. It's through the computer.

So I voted yes, and I must say that as an AD specialist, I must admit that I'm envious of my ALS colleagues for having such a promising prognostic biomarker, NfL. That seems to be linked to clinical and functional outcomes, at least among the patients with this rare causal mutation, but also, hopefully, also more generally across the entirety of the ALS population. I was convinced by

the data, and voted yes.

DR. MONTINE: Thank you.

Mr. Wilson?

MR. WILSON: Thank you. This is Michael Wilson, and I also voted yes. Maybe NfL could be used for getting patients diagnosed sooner and get them ahead to treatment earlier. Thank you.

DR. MONTINE: Thank you.

Dr. Mielke?

DR. MIELKE: Yes. I also voted yes, based on my previous comments, as well as the totality of the data.

DR. MONTINE: Thank you.

Dr. Kryscio?

DR. KRYSCIO: Yes. It's Dick Kryscio. I voted yes for reasons already stated. Thank you.

DR. MONTINE: Thank you.

Dr. Alexander?

DR. ALEXANDER: Yes. It's Robert Alexander. I voted yes. I thought there was sufficient evidence that NfL could be a reasonably likely surrogate. There were clear reductions of NfL by

tofersen, both in the CSF NfL and plasma NfL. Then taking into account all the caveats from the FDA statistical group, I think a review of the 52-week data and comparing the early-start and later-start subjects was supportive that there's a clinical benefit of that NfL reduction. Thank you.

DR. MONTINE: Thank you.

Dr. Simuni?

DR. SIMUNI: I voted yes for the reasons that I have stated previously, so I don't think that I need to reiterate.

DR. MONTINE: Thank you.

Then my name is Thomas Montine. I voted yes for all the reasons that had been previously stated.

We will now move on to question 3. Question 3 is a discussion point. Discuss the strengths and limitations of the available clinical data from the placebo-controlled study and long-term extension regarding the effectiveness of tofersen for SOD1 ALS.

Do the panel members have any comments or

questions about the wording of this discussion point?

(No response.)

DR. MONTINE: If there are no questions or comments concerning the wording of the question, we will now open the question to discussion.

Dr. Alexander, I think your hand was up first.

DR. ALEXANDER: Thanks, Dr. Montine. It's Robert Alexander. I just want a clarification that the point of this discussion and the subsequent question is whether we believe that the data supports full approval. Thank you.

DR. MONTINE: Thank you.

Dr. Apostolova?

DR. APOSTOLOVA: Yes. My concern with the long-term extension would be that there is no placebo group, and there is quite a bit of heterogeneity in the survival of patients. We heard up to 10 years, so it would be really, really hard to know for a fact that the drug is truly working, unless, I guess, NfL outperforms and is

closely linked to survival as well, in terms of rate of change, and rate of baseline, and all of that; so more evidence coming from multiple trials. Pre-competitive analysis of existing data might be really, really useful to clarify that point.

DR. MONTINE: Thank you.

Mr. Wilson?

MR. WILSON: Yes. This is Michael Wilson, and something that just kind of struck me going through all the testimonies, I really haven't found any actual experts in ALS that are speaking out against tofersen. Actually, multiple practicing neurologists provided written testimony for approval. That seems kind of different from previous therapies where there was more mixed methods, so I thought that was interesting. Thank you.

DR. MONTINE: Thank you.

Dr. Gold?

DR. GOLD: Yes. Hi. Thank you. Dr. Gold.

As I was listening to the presentations of both the sponsor and FDA, and obviously the very

emotional testimonials, I guess part of what I'm thinking through is the design of this study must have been very carefully thought through and discussed with both clinical experts and regulators.

I guess I'm just a little bit surprised at the fact that all this modeling that took place to predict rapid progression and what was known about the mutations, it just seems a little bit kind of, I don't know, maybe naïve, or just, "Hey, look. We did all this work, and guess what? It didn't pan out."

Rate of progression that's reported in the study, at least in the fast progressors, is remarkably lower than what was planned, so of course it renders the study as generally under par, so that's not a surprise. So I'm trying to figure out if I'm the only one that's kind of struggling with how much of this was known and how much of this was really is this really such recent emerging data, that when the study was being designed, the assumptions that were made were really on solid

ground? I think that's what I've been struggling with.

I guess those of us in drug development, we often hear this. We make all sorts of assumptions in planning a study, and then when we run it, things don't pan out; I mean, either too much placebo, or not enough placebo, or whatever it is. But it struck me that all the modeling that went in, and all the data that was available from a myriad of ALS studies, we seemed to have really missed the mark on basic assumptions.

DR. MONTINE: Thank you. I had the same question. So if I may, Dr. Gold, could we direct your question to the Biogen team and ask them to respond?

DR. GOLD: Yes, absolutely, please. Thank you.

DR. MONTINE: Thank you.

DR. FRADETTE: This is Stephanie Fradette from Biogen. I'll start by saying we did miss the mark. We designed the study based on what we knew at the time, but admittedly, this is one of the

many implications of the rarity of SOD1 ALS. Slide up, please, if we're able to, Chair; if not, that's ok.

As I noted earlier, the data that we had in hand to inform the assumptions around the decline in the placebo arm was from 12 people, 12 people that matched the eligibility criteria for the study, so certainly not intended to be an excuse but an acknowledgement of why things were so different from what we had anticipated.

I'd say that the utility of neurofilament to control for heterogeneity instead of mutation type and the pre-randomization slope perhaps should have been obvious at the time that we were designing the study, but you can see on the slide that so much of the work, particularly the work done to compare the prognostic strength of neurofilament to other characteristics like progression rate, has happened more recently within the last few years or so.

So it's sort of a combination of the limited data set and the evolving understanding of neurofilament over time, but I'm encouraged to see

how much of these learnings have already been put into place across other clinical trials, including Biogen trials, and other trials as well. So we'll look forward to better trials designed in the future. Thank you.

DR. MONTINE: Thank you.

Dr. Weisman?

DR. WEISMAN: Hi. I just think it would help us discuss matters by maybe rephrasing the question, and as the first question, does it work in 6 months? And the answer's clearly no, but does the total trial data set tell us that it works after 6 months? I know that there are problems with that, but I really want to say yes when we're looking at all of the data.

Anyway, I just think we should break this down into two questions. The 6-month time point, clearly not sufficient, failed trial, but after that, my inclination is yes. Thank you.

DR. MONTINE: Thank you for your analysis.

DR. WEISMAN: Yes. I'll defer to anybody else to comment and take a contradictory position

and try to hash this out.

DR. MONTINE: Right. Thank you.

Dr. Simuni?

DR. SIMUNI: Tanya Simuni, Northwestern. So we are being asked to adjudicate as advisors on the question of does the provided data in entirety, double-blind and open-label extension studies, provide convincing evidence of effectiveness, and "convincing" is the word that the regulatory body will take into consideration, for consideration of the full approval.

So the short answer, no. I think that the field and the world should celebrate the data as the major milestone, the biomarker readout, the development, and the signal of clinical effectiveness with a longer duration of the follow-up, but to adjudicate on the question of convincing data supporting efficacy, we need more data. So that's my interpretation.

DR. MONTINE: Thank you.

I may take a moment then to try to summarize what I've heard so far, and then return it back to

the panel.

Obviously, in the context of an ultra rare disease, this was a large study but had some serious design flaws. In retrospect, as the Biogen team said, we've learned lessons but still there are design flaws that have complicated the study.

I believe it was Dr. Weisman who I think made the reasonable point of considering them as two separate entities, two separate considerations, the placebo-controlled study that clearly failed, but then the open-label extension of where we do begin to see a signal; and to paraphrase what Dr. Simuni just said, a signal that's suggestive but not conclusive.

So with that as a summary, I'll return now to hands that are up.

Dr. Kryscio, please, if you could comment on the comments that have been made so far, then whatever else you wish to add.

DR. KRYSCIO: Yes. I believe, with Dr. Simuni, in a sense that we have too few events, hard endpoints, which would be survival and/or

unpermanent ventilation, to back a convincing result here. So that's my take on it.

We need more information, and time will kind of help us a little bit. And I know it's kind of biased, but it may be the only information we get, but things can change on a dime in these situations. When you have a small number of events, things could change radically as the number of events are accrued. So I think the word "convincing" has me a little worried in this second question.

DR. MONTINE: Dr. Alexander?

DR. ALEXANDER: Yes. Hi. It's Robert Alexander. I just want to say I agree with Dr. Simuni's assessment that the data doesn't meet the standard of convincing evidence of efficacy. You can speculate that maybe if the duration of the double-blind period had been longer, or if NfL had been used as a covariate, you might have seen a clearer signal, but that wasn't done, and there's no real do-over here.

I just want to express one concern. We

heard from the sponsor that there were 8 subjects where they weren't able to determine from the post-withdrawal vital status data whether or not they were alive or not. And given the small numbers, there are only 23 deaths, I guess at least, that were recorded in the briefing document. That could make a big difference.

So I think it would be important going forward to really understand what happened to a hundred percent of the subjects who were in trial, if that's at all possible. Thank you.

(Pause.)

DR. SEO: Hi, Dr. Montine. This is Jessica. If you're speaking, we cannot hear you. Would you mind checking if you're muted?

DR. MONTINE: Yes, sorry. Excuse me. I did that again.

Dr. Weisman, could you, please?

DR. WEISMAN: Yes. Given the complexity, I'd say it's very appropriate to ask for more data, but I would say what new data would be convincing in that case because I would be concerned that

another randomized-controlled trial is not feasible. It doesn't have equipoise. So would following the open-label folks be what we're looking for in terms of more data?

(Pause.)

DR. ALEXANDER: If I may, it's Robert Alexander. I don't think the question is what additional data; the question is, does existing data provide convincing evidence? I think we should restrict ourselves to that. We heard from Dr. Buracchio about the FDA's thoughts about what data could be used to confirm whether there's a clinical benefit, but I think the question on the table is, the data we have in front of us, is that convincing?

DR. WEISMAN: Okay, fair enough. Fair enough.

DR. MONTINE: Thank you. That is the question, the strengths and limitations of the available clinical data.

Dr. Mielke, I believe you're next.

DR. MIELKE: Yes. Thank you. Michelle

Mielke. I agree with the direction of the discussion and the focus on the convincing evidence. I think it is important to highlight, though -- I mean, given some of the limitations of the analyses, there are suggestions that there may really be a clinical benefit in a disease that is highly progressive and very fatal. So in that regard, the clinical data over the 52 weeks are really exciting.

I do agree that there is a limited number of events, and it would have been more helpful, in terms of convincing evidence, if there was more data. So I guess, personally, I'm struggling with the word "convincing" on this because I think there is evidence suggesting potential clinical benefit, but does it cross a convincing line or not; again, that's a little bit of what I'm struggling with.

DR. MONTINE: Thank you.

Dr. Kryscio, you're next.

DR. KRYSCIO: Sorry. I didn't mean to raise my hand, but I would say, what kind of data can we expect down the road? While it's clear we'll get

more events in this OLE, open-label extension, and that will be very helpful, then you can look down at the ATLAS study, which while it's not with patients that actually are symptomatic or asymptomatic, there will be a lot of useful information there.

So I'm in agreement with the group that right at the moment, the issue is whether the current data is convincing or not, and I just don't see it as being convincing.

DR. MONTINE: Thank you.

Dr. Gold?

DR. GOLD: Just one quick comment. Compared to other conditions, where open-label data are, really, I would say of questionable value, the natural history here is so clear that it's hard to imagine that even data obtained from routine clinical practice would not be of value.

I understand the concern about equipoise for a placebo-controlled trial, and I think on the facts of what's available, I would have difficulty convincing a patient to enroll in a

placebo-controlled trial. But in a well-designed, open-label, real-world study, where we can follow appropriate biomarkers and clinically relevant measures, I think that's a viable route with this patient population. I don't think any of the patients or families that testified would have objected to providing additional data. Thank you.

DR. MONTINE: Thank you.

DR. BURACCHIO: Hi. Dr. Montine, this is Teresa Buracchio. Would I be able to speak? I'm hearing a number of questions about the word "convincing," and I just wanted to address that, if I could.

Would that be alright?

DR. MONTINE: Oh, please do.

DR. BURACCHIO: Okay.

On the next slide, we do ask about convincing data, and just to clarify, that would be referring to would this be suitable for a full approval of the application. So that is where we are heading to that comment.

In the word "convincing," I think we do take

into consideration that is where the role of regulatory flexibility comes in. So our first substantial evidence of effectiveness is a qualitative assessment that relies on scientific judgment, and you do want to look at the data in the context of the fact that it is a severe, serious disease, a fatal disease. It's very rare and there is unmet need.

So the word "convincing" should be considered, I think, as another way of saying substantial evidence of effectiveness, but also taking into account the context of the unmet need and the seriousness of this disease.

DR. MONTINE: Thank you very much.

Are there any further comments from panel members?

(No response.)

DR. MONTINE: I'll summarize, and perhaps others will have comments on the summary. We're taking into consideration the strengths and weaknesses of available clinical data from both placebo-controlled studies and the long-term

extension regarding effectiveness of tofersen in SOD1 ALS.

I think I heard a strong consensus that the first part of that question, the clinical data from the placebo-controlled study did not show effectiveness, but considered along with the long-term extension, adjectives were exciting, suggestive, encouraging, but not conclusive, and not conclusive for a variety of reasons that were raised by multiple members of the panel.

Does anyone on the panel have a strong opinion about that summary, either one way or the other?

(No response.)

DR. MONTINE: Okay.

If there's no further discussion of this question, we will now move on to question 4, which is a voting question. I'll read this into the record, the question 4 vote.

Does the clinical data from the placebo-controlled study and available long-term extension study results, with additional supporting

results from the effects of relevant biomarkers, i.e., changes in plasma neurofilament light concentration and/or reductions in SOD1, provide convincing evidence of the effectiveness of tofersen in the treatment of patients with SOD1 ALS?

Does anyone on the panel have questions or comments about the wording of this voting question?

(No response.)

DR. WEISMAN: I think we've talked about that quite a bit, but the sticking point is this word "convincing," if we could get rid of that or change it to something maybe more appropriate, or are we going to stick with convincing as previously defined? This is Dave Weisman. Sorry.

DR. MONTINE: Thank you, Dr. Weisman.

Dr. Buracchio, I think I have to hand that to you.

DR. BURACCHIO: Well, as I said, I think we could consider this. If you want to change "convincing" to provide substantial evidence of effectiveness, that would be an appropriate

substitution. That is a regulatory term, though, so I'm not sure if the panel finds that more or less comfortable for that wording, but that would be another way of interpreting the wording.

DR. MONTINE: If I could just clarify then, we can read this either as provide convincing evidence or substituting the phrase that you just said. We can use either of those questions?

DR. BURACCHIO: Yes. I think substantial evidence of effectiveness would be an appropriate substitution, if that is more helpful.

DR. MONTINE: Is that clear to the panel members?

DR. SIMUNI: This is Tanya Simuni.

Dr. Buracchio, can you please clarify or repeat what you've said before? Substantial evidence in the framework of regulatory definition --

DR. BURACCHIO: Right.

DR. SIMUNI: -- to support full approval? Is that a correct interpretation?

DR. BURACCHIO: To provide substantial

evidence of effectiveness of tofersen for full approval; yes, that would be to support full approval in the treatment of patients with SOD1 ALS.

DR. SIMUNI: Okay. Thank you very much.

DR. BURACCHIO: I'll just, again, clarify that we can accept some uncertainty in this. So when we say convincing or substantial evidence of effectiveness, that's not 100 percent. I absolutely believe there can be some level of uncertainty in this setting, and taking into account, as I said, the seriousness of the disease, and the rarity, and the unmet need. But the bar is to meet substantial evidence of effectiveness.

DR. MONTINE: Are there any other questions about the wording of this voting question from the panel?

(No response.)

DR. MONTINE: If there are no questions or comments, no further questions or comments, concerning the wording of the question, we will now begin the voting on question 4.

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: Again, voting has closed and is now complete. The vote results are displayed. I will read the vote totals into the record. The chairperson will go down the list, and each voting member will state their name and their vote into the record. You can also state the reason why you voted as you did, if you want to.

There were 3 yeses, 5 noes, and 1 abstention.

Dr. Montine?

(No response.)

DR. SEO: Dr. Montine, this is Jessica.

DR. MONTINE: My apology.

DR. SEO: You're fine.

DR. MONTINE: 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 for your vote, if you wish to.

We will start with Dr. Weisman.

DR. WEISMAN: I agonized over my decision, and I really respect people who voted no. I think that the odds are extremely high that this drug works. I guess I really worry about the consequences of an accelerated approval maybe as a neurologist, where payers will not cover this drug and consider it experimental, which I think would be a big problem clinically. So thank you very much.

DR. MONTINE: Thank you.

Dr. Romero?

DR. ROMERO: Yes. Thank you. My abstention has to do with the pre-competitive and non-competitive nature of my work. Thank you.

DR. MONTINE: Thank you.

Dr. Apostolova?

DR. APOSTOLOVA: Yes. The trial that was

presented unfortunately did not meet the primary and secondary endpoints. Thus, my answer to this very question is no.

DR. MONTINE: Thank you.

Dr. Wilson?

MR. WILSON: Yes. This is Michael Wilson. I voted yes. I echo Dr. Weisman's comments, and I'd also say I think substantial evidence was met. If you think about your late-start group stayed on placebo, I think that would have been an even wider spread in the data. Thank you.

DR. MONTINE: Thank you.

Dr. Mielke?

DR. MIELKE: Yes. Michelle Mielke. I voted yes as well. I agonized over this. Certainly all of the data is not fully conclusive, but there are several aspects of the data that do suggest strong clinical evidence. And again, my decision also weighed in the fact that this really is an unmet need, and ALS is a very serious disease. So the fact that some people may be stalling in terms of their progression or possibly improving is very

promising. Thank you.

DR. MONTINE: Thank you.

Dr. Kryscio?

DR. KRYSCIO: Yes. It's Richard Kryscio. I voted no. The trial did not meet its goals and their prespecified hypotheses. We heard from the sponsor that they didn't know a whole lot about the natural history of the disease, and although we're going to have data that's based on the open-label extension, we will have more events to find out if the positive results on the biomarker, the neurofilament light, actually translates into a true clinical benefit, which I don't see right now.

DR. MONTINE: Thank you.

Dr. Alexander?

DR. ALEXANDER: Yes. This is Robert Alexander. I voted no. I think it meets the evidentiary standards for accelerated approval, but not for full approval, which is essentially what we're being asked here. Thank you.

DR. MONTINE: Thank you.

Dr. Simuni?

(No response.)

DR. MONTINE: Dr. Simuni, please.

(No response.)

DR. MONTINE: Tanya, you may be muted.

(No response.)

DR. MONTINE: Dr. Simuni, can you hear me?

(No response.)

DR. MONTINE: Jessica, may I go on and cycle back?

DR. SEO: Hi, Dr. Montine. This is Jessica. Yes, why don't you go ahead and let's circle back to Dr. Simuni, and give her a chance to connect her audio. Thank you.

DR. MONTINE: My name is Thomas Montine. I voted no for the reasons given above. As Dr. Alexander succinctly put, I think it meets the standards expected for accelerated approval, but not for traditional approval. And like others, this was a difficult decision. What weighed heavily on me was the negative outcomes of the placebo-controlled fraction portion of the data.

Dr. Simuni?

(No response.)

DR. MONTINE: Jessica, may I --

DR. SEO: Hi, Dr. Montine.

Yes. Dr. Simuni, in Adobe Connect, it appears your microphone is muted. If you could select the unmute option and try to speak, and we'll see if we can hear you.

(No response.)

DR. MONTINE: Well, at minimum, for Dr. Simuni, I can read her vote into the record. She voted no.

I don't know quite what to do, Jessica, so please advise.

DR. SEO: Thank you for reading her vote into the record, Dr. Montine. Unfortunately, it appears we're not able to reconnect her audio to hear her provide any explanation or reasoning, but if you'd like to move on, perhaps we can return to it at a later point.

DR. MONTINE: Okay.

We will now move on to question 5. Question 5 for discussion, discuss the overall

benefit-risk assessment for tofersen in patients with SOD1 ALS. If the available evidence supports a benefit, discuss if the risks appear to be acceptable given the observed treatment benefit. If the benefit-risk assessment does not appear favorable, discuss what additional data would be needed for the benefit-risk assessment to be favorable.

Does the panel have any questions or comments about the wording of this question?

(No response.)

DR. MONTINE: If there are no questions or comments concerning the wording of the question, we will now open the question to the panel for discussion.

Dr. Alexander, please.

DR. ALEXANDER: Yes. It's Robert Alexander. I'll start.

In my view, the overall benefit-risk is favorable. There are some serious neurologic adverse events, but they're fortunately relatively infrequent and appear to be manageable, and in the

context of the illness itself I think don't stand in the way of this drug being used. Thank you.

DR. MONTINE: Thank you. That was, I think, in my opinion, an excellent summary. I agree with you entirely.

I believe next is Mr. Wilson.

MR. WILSON: Yes. This is Michael Wilson, and I also just wanted to say what Dr. Alexander said was exactly what I was thinking to say. The community is going to give credit [indiscernible] to lumbar puncture given what our bodies are going through already, so I don't see much of an issue. Thank you.

DR. MONTINE: Thank you.

Dr. Weisman, I was unclear if you wished to raise your hand or not.

DR. WEISMAN: I just wanted to reiterate the same point, but it's been said, so I appreciate it.

DR. MONTINE: Great. Thank you.

DR. SEO: Dr. Montine, this is Jessica. I apologize for interrupting. We'd like to have you call for a 5-minute break, please, while we work to

get some of the panel members connected. They're having some technical difficulties.

DR. MONTINE: Okay.

So our apologies to everyone, but we need to take a 5-minute break. Let's make it 7 minutes. We'll come back at 5:25.

(Whereupon, at 5:18 p.m., a recess was taken.)

DR. MONTINE: Thank you, Jessica. May we please reconvene, then?

(No response.)

DR. MONTINE: Jessica, I think I'll start again by reading this question because I'm not exactly sure where people dropped off. Is that ok?

DR. SEO: Yes, that would be fine, Dr. Montine.

DR. MONTINE: Okay

Question 5 is for discussion. Discuss the overall benefit-risk assessment for tofersen in patients with amyotrophic lateral sclerosis secondary to a mutation in SOD1. If the available evidence supports a benefit, discuss if the risks

appear to be acceptable given the observed treatment benefit. If the benefit-risk assessment does not appear favorable, discuss what additional data would be needed for the benefit-risk assessment to be favorable.

Are there any questions from the panel about the wording of this question?

(No response.)

DR. MONTINE: If there are no questions or comments concerning the wording of the question, we will now open the question to discussion.

I will return to Dr. Alexander, who made a terrific summary of his opinion that many of us were agreeing with before.

Robert, if you wouldn't mind restating your assessment.

DR. ALEXANDER: Sure. It's Robert Alexander. I said that I felt that the overall risk-benefit was favorable; that while there were infrequent but serious neurologic adverse events, they appeared to be manageable, and that the overall adverse event profile in the context of the

seriousness of the illness was supportive of a favorable risk-benefit assessment. Thank you.

DR. MONTINE: Thank you again, and then Dr. Weisman and I conferred with that assessment.

Would any other panel member -- Mr. Wilson, your hand is up. No, excuse me. I misread it.

Dr. Gold, your hand is up.

DR. GOLD: Yes. Thank you. It's Dr. Gold again. Just one quick comment, and then --

FEMALE VOICE: Excuse me, please, Dr. Gold; just one quick comment.

DR. GOLD: Please, go ahead.

(No response.)

DR. GOLD: Sorry. Can you hear me?

DR. MONTINE: I can, Dr. Gold. I'm not sure what that was.

DR. GOLD: Yes. Just one quick comment, which is that we should guard against any paternalism here about adverse events. Those of us who worked in other areas with rapidly progressive diseases, I think patients here are willing to undertake huge amounts of personal risk because of

what they're facing, so just a vote of confidence in patients and their judgment in terms of what they're willing to endure.

The other part is, because of the route of administration, it just means to me there's going to have to be, based on the safety profile, really kind of persnickety attention to training and procedures to administer this compound. This is not a once-in-a-lifetime LP for diagnostic purposes. The adverse event, the neurological ones, may be post and parcel with the target, but there were some procedural adverse events. I think those could be mitigated against with careful training, but overall, the benefit to me was quite positive.

DR. MONTINE: Thank you. Excellent points.

Other panel members wish to comment?

DR. WEISMAN: Just a quick question, I guess, for -- I really don't know who this should go to, but there are different incidents of post-LP headaches, depending on the needle that is used. Were investigators encouraged to use Sprotte

needles that have a much lower incidence? Because if that's in clinical practice with a recommendation of a Sprotte needle, that would very much reduce the post-LP headaches. Thank you.

DR. MONTINE: Thank you.

Dr. Weisman, may I --

DR. FRADETTE: Would you --

DR. MONTINE: Excuse me? Yes?

DR. FRADETTE: Dr. Montine --

DR. MONTINE: That's fine.

DR. FRADETTE: -- apologies for interrupting. This is Stephanie Fradette from Biogen. I wasn't sure if you wanted the Biogen team to comment on that question.

DR. MONTINE: That's what I was asking. So why don't you please go ahead? Thank you, Stephanie.

DR. FRADETTE: Sure. I'll ask Dr. Fanning to comment. Thank you.

DR. FANNING: This is Laura Fanning from Biogen. The answer is yes. In the clinical trials, the instruction or recommendation was to

use a non-cutting needle such as a Sprotte. I don't actually recall the exact gauge, but not to -- so a 22-gauge; actually I'm being reminded. And yes, that does reduce but not eliminate the risk of some procedure-related side effects. So I think that would certainly be supported by the data that we have. Thank you.

DR. MONTINE: Thank you.

Dr. Apostolova?

DR. APOSTOLOVA: Can you hear me? I'm connected via a third method.

DR. MONTINE: I can hear you.

Good. Okay.

Overall, we're talking about a devastating disease that is uniformly lethal, so I would concur with everything I heard prior to my statement, that the benefit-risk assessment in such a condition is a totally different issue, and being an intrathecal injection, some of it is to be expected. But I do believe the patients will be more than willing to endure the risk of intrathecal injection in order to benefit and have prolonged survival.

DR. MONTINE: Thank you, Dr. Apostolova.

Dr. Weisman, please.

DR. WEISMAN: I'm sorry. My hand was up from the previous question, and I didn't put it down. I just did now. I'm sorry.

DR. MONTINE: That's no problem at all. Thank you.

Would any other member of the panel descend from what's so far is unanimous opinion, that the benefits outweigh the risks; and obviously there are some serious adverse events, and we should take all effort that we can to minimize them?

(No response.)

DR. MONTINE: If there's no further discussion on this question, we will move to adjournment of this meeting. Before we adjourn, are there any last comments from the FDA?

DR. BURACCHIO: Hi. Yes. This is Teresa Buracchio. I would just like to take this opportunity to thank the panel for their very illuminating comments. You've really been very thoughtful about the data in front of you today. I

know this has been a challenging meeting, and a long meeting, but we really appreciate your input. It's been incredibly helpful to us. And also, I didn't get to thank the patients of the open public hearing portion, and I would like to thank all of the patients who shared their stories with us today.

Thank you, Dr. Montine, for chairing a successful AC. Thank you.

Adjournment

DR. MONTINE: Thank you, Dr. Buracchio.

I know I can speak for the entire panel to thank the patients and other individuals who spoke at the public session. It's invaluable to have your insight and testimonial. Of course, we would like to thank the FDA staff for always preparing what are clear, concise analyses of the data and terrific presentations that help us understand the issues. I'd also like to thank the team from Biogen for the packet of material that they presented, and also for their very clear presentations this morning. And finally, thank you

to my fellow panel members for your time and thoughtfulness.

We will now adjourn the meeting. Thank you.

(Whereupon, at 5:31 p.m., the meeting was adjourned.)