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Center for Biologics Evaluation and Research (CBER)

75th Meeting of the Cellular, Tissue, and Gene Therapies Advisory Committee (CTGTAC)

Zoom Video Conference

September 27, 2023

This transcript appears as received from the commercial transcribing service after inclusion of minor corrections to typographical and factual errors recommended by the DFO.

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Participants

Members			
Chair (Acting)	Tabassum (Taby) Ahsan, Ph.D.	Vice-President, Cell Therapy Operations, City of Hope	Duarte, CA
Consumer Representative	Kathleen O'Sullivan-Fortin, Esq.	Founder, ALD Connect, Inc.	Middleton, MA
	Donald B. Kohn, M.D.	Distinguished Professor, David Geffen School of Medicine at UCLA	Los Angeles, CA
	Wendy B. London, Ph.D.	Associate Professor of Pediatrics, Boston Children's Hospital/Dana-Farber Cancer Institute, Harvard Medical School	Boston, MA
	Nirali N. Shah M.D., M.H.Sc.	Head, Hematologic Malignancies Section, National Cancer Institute	Bethesda, MD
	Gil I. Wolfe, M.D.	Professor and Chairman of Neurology, Jacobs School of Medicine and Biomedical Sciences, University at Buffalo/SUNY	Buffalo, NY
	Joseph Wu, M.D., Ph.D.	Director, Stanford Cardiovascular Institute; Professor of Medicine and Radiology, Stanford University	Stanford, CA
Temporary Voting Members			
	G. Caleb Alexander, M.D., M.S	Professor, Bloomberg School of Public Health, Johns Hopkins University	Baltimore, MD
Patient Representative	Andrew Buckley, M.B.A., J.D.	Patient Representative	Deer Park, IL
	Kenneth Fischbeck, M.D.	Distinguished Investigator, Neurogenetics Branch, Division of Intramural Research, National Institute of Neurological Disorders and Stroke, NIH	Bethesda, MD
	Nicholas E. Johnson, M.D., M.S.C.I., F.A.A.N.	Associate Professor of Neurology, Human Molecular Genetics, Virginia Commonwealth University	Richmond, VA
	Richard Kryscio, Ph.D.	Professor, University of Kentucky	Lexington, KY
	Lisa Lee, Ph.D.	Research Professor, Associate Vice President for Research and Innovation, Virginia Tech	Blacksburg, VA

	Jun Li, M.D., Ph.D., F.A.N.A., F.A.A.N.	Professor and Chair, Department of Neurology, Houston Methodist Hospital, Weill Cornell Medical College	Houston, TX
	Ronald Liem, Ph.D.	Professor of Pathology and Cell Biology, Columbia University School of Medicine	New York, NY
	Jan A. Nolta, Ph.D.	Director, Stem Cell Program and Gene Therapy Center; Scientific Director, UC Davis GMP Facility Institute for Regenerative Cures, University of California Davis Health	Sacramento, CA
	Rajiv R. Ratan, M.D., Ph.D.	Winifred Masterson Burke Professor of Weill Cornell; CEO, Burke Neurological Institute	White Plains, NY
	Lynn A. Raymond, M.D., Ph.D.	Director, Djavad Mowafaghian Centre for Brain Health	Vancouver, BC
Temporary Non-Voting Member			
	Michael Gold, M.S., M.D.	Acting Industry Representative; Chief Medical Officer, Neumora Therapeutics	Watertown, MA
FDA Participants			
	Peter W. Marks, M.D., Ph.D.	Director, CBER, FDA	Silver Spring, MD
Speaker	Celia Witten, Ph.D., M.D.	Deputy Director, CBER, FDA	Silver Spring, MD
	Nicole Verdun, M.D.	Director, Office of Therapeutic Products (OTP), CBER, FDA	Silver Spring, MD
	Leila P. Hann	Associate Director for Policy, OTP, CBER, FDA	Silver Spring, MD
Speaker	Tom Finn, Ph.D.	BLA Chair and Chemistry, Manufacturing, and Controls (CMC) Reviewer, Office of Cellular Therapy and Human Tissue CMC, Division of Cell Therapy, OTP, CBER, FDA	Silver Spring, MD
Speaker	Xue (Mary) Lin, Ph.D.	Statistical Reviewer, Office of Biostatistics and Pharmacovigilance, Division of Biostatistics, CBER, FDA	Silver Spring, MD
Speaker	Gumei Liu, M.D., Ph.D.	Clinical Reviewer, Office of Clinical Evaluation, Division of Clinical Evaluation and General Medicine, OTP, CBER, FDA	Silver Spring, MD
Speaker	Rosa Sherafat-Kazemzadeh, M.D.	Clinical Team Leader, Office of Clinical Evaluation, Division of	Silver Spring, MD

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Speaker	Xiaofei Wang, Ph.D.	Clinical Pharmacology Reviewer, OCE, DCEGM, OTP, CBER, FDA	Silver Spring, MD
Designated Federal Officer (DFO)	Marie DeGregorio	Division of Scientific Advisors and Consultants (DSAC), CBER, FDA	Silver Spring, MD
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Committee Management Officer	LaShawn Marks	DSAC, CBER, FDA	Silver Spring, MD
Committee Management Officer	Joanne Lipkind, M.S.	DSAC, CBER, FDA	Silver Spring, MD
Director	Prabhakara Atreya, Ph.D.	DSAC, CBER, FDA	Silver Spring, MD
Guest Speaker			
Guest Speaker	Evan Y. Snyder, M.D., Ph.D., F.A.A.P.	Director, Center for Stem Cells and Regenerative Medicine Professor, Human Genetics Program Sanford Burnham Prebys Medical Discovery Institute	La Jolla, CA
Applicant Presenters			
	Stacy Lindborg, Ph.D.	Co-Chief Executive Officer, BrainStorm Cell Therapeutics	
	Anthony J. Windebank, M.D.	Judith and Jean Pape Adams Professor; Faculty Development Chair, Department of Neurology, Mayo Clinic	
	Lee-Jen Wei, Ph.D.	Professor of Biostatistics, Harvard University	
	Nathan Staff, M.D., Ph.D.	Professor of Neurology; Research Chair, Department of Neurology, Mayo Clinic	
	Robert Bowser, Ph.D.	Chief Scientific Officer; Chair, Department of Translational Neuroscience, Barrow Neurological Institute	
	Kirk Taylor, M.D.	Executive Vice President, Chief Medical Officer, BrainStorm Cell Therapeutics	
Open Public Hearing Speakers			

Mandi Bailey	
Andrea Goodman, M.S.W., M.P.H.	CEO of "I Am ALS"
Philip Green	
Robert Hebron	
Mitze Klingenberg, B.S.N., R.N.	
Joe Morris	
Ajay Sampat, M.D.	Associate Clinical Professor of Neurology, University of California Davis
Kandy Simons	
Josh and Paula Smith	
Amanda Stevens	
Michael Abrams, M.P.H., Ph.D.	Senior Health Researcher from the Public Citizen Health Research Group
Jeffrey A. Cohen, M.D.	Director of Experimental Therapeutics at the Cleveland Clinic Mellen MS Center
Brooke Eby	
Ron Hoffman	Founder and Executive Director, Compassionate Care ALS
Professor Dimitrios Karussis, M.D., Ph.D.	Director of the Neuroimmunology and Cell Therapies Unit at Hadassah University Hospital; Jerusalem, Israel
Brian Wallach	
Dr. Diana Zuckerman	President of the National Center for Health Research

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Opening Remarks: Call to Order and Welcome

Dr. Ahsan: Good morning, everyone. I'd like to welcome the members of the committee and the participants in the public to the 75th meeting of the Cellular Tissue and Gene Therapies Advisory Committee for the Center for Biologics Evaluation and Research at the Food and Drug Administration. Today is September 27th, 2023, and the committee will meet an open session to discuss and make recommendations on BLA 125782 From Brainstorm Cell Therapeutics for debamestrocel, which is an autologous, bone-marrow-derived MSC induced to secrete neurotrophic factors called NurOwn. The applicant has requested an indication for the treatment of mild to moderate ALS. At various points during the day, there will be opportunities for questions and comments. If you'd like to be recognized, please use the raise your hand feature on Zoom and turn your camera on. And once I call upon you, you can unmute to make your comment or ask your question. Please reserve the chat function just for technical AV issues. And so, with that, I'd like to introduce Marie DeGregorio, the Designated Federal Officer for today's meeting for a few administrative aspects.

Administrative Announcements, Roll Call, Introduction of Committee, Conflict of Interest Statement

Ms. DeGregorio: Thank you, Dr Ahsan. Good morning, everyone. This is Marie DeGregorio, and it is my great honor to serve as the Designated Federal Officer, i.e. DFO, for today's 75th Cellular Tissue and Gene Therapies Advisory Committee meeting. On behalf of the FDA, the Center for Biologics Evaluation and Research and the Committee, I'm happy to welcome you for today's virtual meeting. Today, the committee will meet in open session to discuss the Biologics License Application, BLA, 125782 from Brainstorm Cell Therapeutics Incorporated. Today's meeting and topic were announced in the Federal Register Notice that was published on July 27th, 2023.

At this time, I would like to acknowledge and thank my Division Director in the Division of Scientific Advisors and Consultants, DSAC, Dr. Prabhakara Atreya and my team, whose contributions have been critical for preparing today's meeting. This includes Lieutenant Commander Cicely Reese, who is alternate DFO for this meeting and who provided excellent support for this meeting. I'd also like to thank Ms. Tonica Burke, Ms. LaShawn Marks, and Ms. Joanne Lipkind, who provided helpful administrative support in preparation of this meeting.

I would now like to acknowledge CBER leadership, including Dr. Peter Marks, Director of CBER and Dr. Celia Witten, Deputy Director of CBER, Dr. Nicole Verdun, the new Director of CBER's Office of Therapeutic Products, OTP, and many other OTP staff who will be serving as speakers and presenters during the day, as indicated on the agenda. On behalf of DSAC, our sincere gratitude also goes to many CBER and FDA staff working very hard behind the scenes, working to ensure that today's virtual meeting will also be a successful one. I also thank all the other FDA staff contributing to today's meeting discussion, some of whom are present and others who may be joining the meeting at other times.

Please direct any press or media questions for today's meeting to FDA's Office of Media Affairs at fdaoma@fda.hhs.gov. I would also like to thank the audiovisual team, Devante Stevenson, Christopher Swett, and Derek Bonner in facilitating the meeting today. The transcriptionists for today's meeting are Ms. Debbie Dellacroce and Ms. Catherine Diaz. Okay, we will begin today's meeting by taking a formal roll call with the committee members and temporary members. When it is your turn, please make sure your video camera is on and you are unmuted. Then, state your first and last name, organization, expertise, or role, and when finished, you may turn your camera off so we may proceed to the next person. Please see the member

roster slides in which we will begin with the chair. Dr. Ahsan, please go ahead when you're ready.

Dr. Ahsan: Thank you, Marie. I'm Tabby Ahsan. I'm Vice President of Cell and Gene Therapy Operations at the City of Hope. I'll be chairing today's meeting. My area of expertise is in translation of therapeutic products of stem cells, tissue engineering, regenerative medicine, and most recently in CAR T.

Ms. DeGregorio: Okay, thank you, Dr. Ahsan. Next, we have Dr. Donald Kohn.

Dr. Kohn: Good morning. I'm Donald Kohn. I'm a Professor at the University of California, Los Angeles, UCLA. I am a Pediatric Bone Marrow Transplant Physician and I perform Gene Therapy Research for blood cell diseases with hematopoietic stem cells.

Ms. DeGregorio: Okay, thank you. Thank you, Dr. Kohn. Next, we have Dr. Wendy London.

Dr. London: Good morning. I am a Biostatistician at Harvard Medical School, Boston Children's Hospital, and Dana Farber Cancer Institute and have expertise in the conduct of clinical trials in children with cancer and blood disorders.

Ms. DeGregorio: Okay. Thank you, Dr. London. Next, we have Ms. Kathleen O'Sullivan-Fortin.

Ms. O'Sullivan-Fortin: Hi, I'm Kathleen O'Sullivan-Fortin. I'm a Co-Founder and a Board Member at ALD Connect. My expertise is in being a patient with a rare neurodegenerative disease and I am the Sitting Consumer Rep for this committee.

Ms. DeGregorio: Okay. Thank you. We'll continue with the rest of our members. Dr. Nirali Shah, please go ahead.

Dr. Shah: Hi, I'm Dr. Nirali Shaw. I work in the Pediatric Oncology Branch at the Intramural Program of the National Cancer Institute. I lead the Hematologic Malignancies Program where

I've been focused on CAR T-Cell-based therapies for children with relapsed refractory leukemias.

Ms. DeGregorio: Okay, thank you. Next, we have Dr. Gil Wolfe.

Dr. Wolfe: Gil Wolfe, I'm Professor and Chair of the Department of Neurology at the University of Buffalo. It's part of the SUNY system. I'm a Neuromuscular Neurologist. My main interest has been immune-mediated neuromuscular disorders. I've been involved with clinical trials pretty much across the spectrum of the disorders.

Ms. DeGregorio: Okay, thank you. Next, we have Dr. Joseph Wu.

Dr. Wu: Good morning. My name is Joseph Wu. I am the Professor and Director of the Stanford Cardiovascular Institute. I'm a Cardiologist. My lab has been interested in basic research and clinical research related to cardiovascular cell tissue and gene therapy as well as organs. Thank you very much.

Ms. De Gregorio: Okay, thank you. Next, we will do a roll call of our temporary voting members, starting with Dr. Caleb Alexander.

Dr. Alexander: Hi, I am a Professor of Epidemiology and Medicine at Johns Hopkins. I'm a Pharmacoepidemiologist and a Practicing Internist. I'm Former Chair of an FDA Peripheral and Central Nervous System Advisory Committee, and I am Principal Investigator of an FDA-funded Center of Excellence and Regulatory Science and Innovation at Johns Hopkins.

Ms. DeGregorio: Okay, thank you. Yeah, next we have Mr. Andrew Buckley, Patient Representative.

Mr. Buckley: Hi, my name is Andrew Buckley, and as mentioned, I'm the patient representative. My area of expertise is simply as an individual living with ALS. Thank you.

Ms. DeGregorio: Thank you. Next, we have Dr. Kenneth Kurt Fischbeck.

Dr. Fischbeck: Hi, this is Kenneth Fischbeck. I'm an Intramural Investigator here at the Neurology Institute in INDS, at the NIH, trained in neurology and we've worked for a long time on hereditary, neurologic, neurodegenerative neuromuscular diseases with disease gene identification, studies of disease mechanisms, and development of treatment in preclinical and early phase clinical studies.

Ms. DeGregorio: Okay, thank you. Next, we have Dr. Michael Gold our alternate industry rep and a non-voting member.

Dr. Gold: Good morning, everybody. I'm Dr. Michael Gold. I'm Chief Medical Officer at Neumora Therapeutics. I'm a Neurologist, Behavioral Neurologist by training, with expertise in neurodegenerative disorders, clinical trials, and drug development.

Ms. DeGregorio: Okay, thank you. Next, we have Dr. Nicholas Johnson.

Dr. Johnson: Hi, I'm Nick Johnson. I'm Vice Chair of Research at Virginia Commonwealth University. I'm a Neuromuscular Neurologist and my primary area of interest is in the Muscular Dystrophies but I do a spectrum of translational and clinical research across neuromuscular conditions.

Ms. DeGregorio: Okay, thank you. Next, we have Dr. Richard Kryscio.

Dr. Kryscio: Yes, good morning. I'm Richard Kryscio. I'm a Professor of Statistics and Biostatistics at the University of Kentucky, and I specialize in neurodegenerative diseases.

Ms. DeGregorio: Okay, thank you. Next, we have Dr. Lisa Lee.

Dr. Lee: Good morning, I'm Lisa Lee, Associate Vice President for Research and Innovation and Director of Scholarly Integrity and Research Compliance at Virginia Tech. I'm also a Professor of Public Health here at the University. My area of expertise is I'm trained as an

Epidemiologist and as a Bioethicist, and so I am serving as the Bioethics Expert here for this panel. Thank you.

Ms. DeGregorio: Okay, thank you. Next is Dr. Li, Jun Li.

Dr. Li: Good morning, everyone. My name is Jun Li. I am the Professor and Chair in the Department of Neurology at Houston Methodist Hospital. My expertise is in prefrontal nerve diseases, myelin biology, and also the biomarker development in neuromuscular diseases, and I'm seeing the patients with a variety of neuromuscular diseases, particularly inherited profound diseases.

Ms. DeGregorio: Okay, thank you. Next, we have Dr. Ronald Liem.

Dr. Liem: Hi. Hi everyone. I'm Ron Liem, I'm Professor of Pathology and Cell Biology at Columbia University Medical School. My research has been on cell and neurobiology of neurofilaments and mutations of neurofilaments.

Ms. DeGregorio: Thank you. Next, we have Dr. Jan Nolta.

Dr. Nolta: Hi, everybody. I'm Jan. I direct the Stem Cell Program in the Gene Therapy Center at the University of California Davis Health in Sacramento. I've worked in stem cell gene therapy for over 30 years translational to clinical trials and our basic research is on mesenchymal stem or stromal cells.

Ms. DeGregorio: Okay, thank you. Next, we have Dr Rajiv Ratan.

Dr. Ratan: Yes, good morning, everybody. I'm Raj Ratan. I'm a Professor of Neurology and Neuroscience at Weill Cornell Medicine. I direct the Burke Neurological Institute. We're focused on brain and spinal repair. I'm involved in basic translational and clinical research efforts focused on protecting and repairing the brain in acute and chronic neurodegenerative diseases.

Ms. DeGregorio: Okay. Thank you. Dr. Lynn Raymond.

Dr. Raymond: Good morning, everyone. I'm a Professor in Psychiatry and Neurology at the University of British Columbia, the Director of the Djavad Mowafaghian Center for Brain Health, where we combine clinical and basic science research to advance translation in many different disorders including ALS. But my expertise is really in Huntington disease, and I do preclinical research, as well as I'm involved in clinical trials that are multi-center for therapies to slow the progression of Huntington disease. Thank you.

Ms. DeGregorio: Okay. Thank you. And finally, we have Dr. Mark Tuszynski.

Dr. Tuszynski: Good morning. I'm Mark Tuszynski. I'm a Physician Scientist in the Department of Neurology and Neurosciences at the University of California, San Diego. I'm the Director of the UCSD Translational Neuroscience Institute, and I do research on stem cells for spinal cord injury and on growth factors for neurodegenerative diseases. I'm the sponsor of a current Phase One clinical trial of beating up gene therapy and Alzheimer's disease. Thank you.

Ms. DeGregorio: Okay, thank you. Dr. Jeffrey Kordower will not serve as a TVM today. Thank you everyone. We will advance to the Conflict of Interest. Okay, so there are a total of 20 participants, 19 voting members, and one non-voting member. Thank you again for your introductions. Before I begin with reading the Conflict-of-Interest statement, I would just like to briefly mention a few housekeeping items related to today's virtual meeting format. For members, speakers, FDA staff, and anyone else joining us in the Zoom room, please keep yourself on mute unless you are speaking to minimize feedback. If you have raised your hand and are called upon to speak by the chair Dr. Ahsan, please turn on your camera, unmute, state your name, and speak slowly and clearly so that your comments are accurately recorded for transcription and captioning. Thank you. I will now proceed with reading the Conflict-of-Interest statement for the public record.

Dated today, September 27 2023. This is the FDA Conflict of Interest Disclosure Statement read by myself, Marie DeGregorio, DFO for DSAC for this committee meeting. The FDA, Food and Drug Administration. is convening virtually September 27, 2023, for the 75th meeting of the Cellular Tissue and Gene Therapies Advisory Committee under the authority of the Federal Advisory Committee Act, FACA, of 1972. Dr. Ahsan is serving as the acting chair for today's meeting. The CTGTAC committee will meet in open session to discuss and make recommendations on Biologics License Application, BLA, 125782 from Brainstorm Cell Therapeutics Incorporated who are debamestrocel autologous bone-marrow-derived mesenchymal stromal cells, induced to secrete neurotrophic factors, NurOwn. The applicant has requested an indication for treatment of mild to moderate amyotrophic lateral sclerosis, ALS. The topic is determined to be a particular matter involving specific parties, PMISP. With the exception of the acting industry representative member, all standing and temporary voting members of CTGTAC are appointed as regular government employees or special government 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 include but are not limited to 18 U. S. code section 208, which is being provided to participants in today's meeting and to the public. Related to the discussions at this meeting, all members and SGE and RGE. consultants of this committee, including the acting industry representative, have been screened for potential financial conflict of interests of their own, as well as those imputed to them, including those of their spouse or minor children and for the purposes of 18 U. S. C. 208, their employers. These interests may include investments, consulting, expert witness testimony, contracts and grants, cooperative research and

development agreements, teaching, speaking, writing, patents and royalties, and primary employment. These may include interests that are current or under negotiation. FDA has determined that all members of this advisory committee, both regular and temporary members, 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 who have financial conflicts of interest when it is determined that the agency's need for a special government employee's services outweighs the potential for a conflict of interest created by the financial interest involved or when the interest of a regular government employee is not so substantial as to be deemed likely to in fact affect the integrity of the services, which the government may expect from the employee. Based on today's agenda and all financial interests reported by committee members and consultants one section 208 waiver was issued for Dr. Jun Li, a special government employee, for his participation in this meeting. The waiver is posted on the FDA website for public disclosure. We have the following consultants serving as temporary voting members: Dr. Caleb Alexander, Mr. Andrew Buckley, Dr. Kenneth Fischbeck, Dr. Nicholas Johnson, Dr. Richard Kryscio, Dr. Lisa Lee, Dr. Jun Li, Dr. Ronald Liem, Dr. Jan Nolta, Dr. Rajiv Ratan, Dr. Lynn Raymond, and Dr. Mark Tuszynski. Among these consultants, Mr. Andrew Buckley is serving as a patient representative and temporary voting member. Patient representatives are appointed special government employees and are screened and cleared prior to their participation in the meeting. They are voting members of the committee. Ms. Kathleen O'Sullivan-Fortin is serving as the Consumer Representative for this committee meeting. Consumer Representatives are appointed special government employees and are screened and cleared prior to their participation in the meeting. They are voting members of the committee. Dr. Michael Gold of Neumora Therapeutics will serve as the acting industry representative for

today's meeting. Industry representatives are not appointed as special government employees and serve as non-voting members of the committee. Industry representatives act on behalf of all related industry and bring general industry perspective to the committee. Industry representatives on this committee are not screened and do not participate in any closed sessions if held. And they do not have voting privileges.

Disclosure of conflicts of interest for guest speakers follows applicable federal laws, regulations, and FDA guidance. FDA encourages all meeting participants, including Open Public Hearing speakers, to advise the committee of any financial relationships that they may have with any affected firms, its products, and if known, its direct competitors. We would like to remind members, consultants, and participants 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 inform the DFO and exclude themselves from such involvement and their exclusion will be noted for the record. This concludes my reading of the Conflicts of Interest Statement for the public record. At this time, I would like to hand over the meeting to Dr. Taby Ahsan. Thank you.

Dr. Ahsan: Thank you, Marie. At this point, I'd like to thank the committee members for their time and effort as relating to helping the FDA evaluate this BLA. And I'd like to thank Marie and the other FDA members who have helped to prepare and organize today's meeting. At this point, we have some opening remarks from Dr. Celia Witten, the Deputy Director of CBER. Dr. Whitten, please turn on your camera and unmute your microphone.

FDA Introduction

Opening Remarks — Dr. Celia Witten

Dr. Witten: Thank you. Good morning. I'd like to welcome our committee members who are joining for this important meeting. Thank you for the time you've taken to review the materials

provided in advance in order to prepare for the discussion today of this application. I'd also like to thank our invited speaker for sharing his expertise in the area of stem cell therapies in the presentation during the morning session. I'd like to thank members of the public who are participating in the Open Public Hearing as well as those members of the public who have contributed to the docket. We're very appreciative of this opportunity to hear your perspective. We are here today to discuss Brainstorm's application for the treatment of mild to moderate amyotrophic lateral sclerosis, ALS. ALS is a progressive and ultimately fatal neurodegenerative disease characterized by progressive weakness and atrophy of skeletal muscle. Most patients die within 3 to 5 years after symptom onset due to respiratory failure, although approximately 10 percent of patients may survive for 10 years or more. Although there have been several drugs approved for ALS over the past several years, there continues to be an urgent need for treatment for this population.

Unfortunately, both the phase-2 and the phase-3 randomized, double-blind, placebo-controlled studies conducted as part of the applicant's development program for this product failed to show efficacy. The regulatory history has been summarized in the briefing document provided by FDA. I want to touch on two items. One aspect of the regulatory history and one recent development relevant to today's discussion. The first is regarding refusal to file and the goal of this public meeting. FDA refused to file a BLA application as the agency made the determination that substantial evidence of effectiveness was lacking and there were important deficiencies in the manufacturing information provided. The applicant chose to file the application over for protest. Although the application was filed over protest, FDA believes that it's important to have a public discussion about the scientific and clinical issues raised in the

application. ALS is a life-threatening disease in need of treatments, and an open public discussion will provide transparency to the issues raised by this application.

The second item I'd like to note is the recent development, which was referred to by the DFO earlier this morning. Last week, the applicant chose to modify the indication they were seeking from indication for treatment of ALS, to an indication for treatment of mild to moderate ALS. Mild to moderate ALS was not defined and the support for the modified indication is based, at least in part, upon an analysis performed by the applicant on a subset of subjects in the pivotal study based on their entry, ALS functional rating scale revised the ALSFRS score. Although FDA's briefing package, which is based on the original indication of treatment of ALS, which was the indication for which the application was submitted, the issues raised in the briefing package are relevant to the subset indication also. It is FDA's position, however, that in this particular case, the subset analysis does not provide substantial evidence of effectiveness. The voting question you're being asked today requests you to vote on whether the data presented here demonstrate substantial evidence of effectiveness for treatment of mild to moderate ALS.

So, before closing, I'd like to spend a moment to discuss what we mean by substantial evidence of effectiveness. There are a range of approaches in terms of trial design and points and types of data and evidence that can meet the statutory requirements for substantial evidence, which can include data from two adequate and well controlled trials, or in some cases, data from one adequate and well controlled trial accompanied by confirmatory evidence. Although the FDA has flexibility when considering the types of data and evidence that can meet the substantial evidence requirement and has exercised this flexibility in particular in rare diseases where there's an unmet need, the statutory standards for substantial evidence of effectiveness apply for the approval of all new drugs. We look forward to the discussion today on the matter before us,

which is important for patients and the applicant as well as for FDA. And now I'll turn it back over to our chair. Thank you.

Dr. Ahsan: Thank you, Dr. Witten for that clarification and explanation of the context of today's meeting. I don't expect there to be so, but if there are any quick clarifying questions? Okay, with that, we'll move on. Dr. Rosa Sherafat will be providing a presentation of the FDA overview of this BLA.

FDA Overview of BLA 125782 for Debamestrocel — Dr. Rosa Sherafat-Kazemzadeh

Dr. Sherafat-Kazemzadeh: Thank you, Dr. Ahsan. Good morning. I am Rosa Sherafat, a clinical team lead in the Office of Clinical Evaluation, Office of Therapeutic Products in the FDA Center for Biologics Evaluation and Research, CBER. On behalf of the FDA review team, I would like to thank the advisory committee chair and panel members, patient representatives, and the applicant, Brainstorm Therapeutics Team and all the patients, families, caregivers, physicians, and providers who will be participating in the Open Public Hearing session or have submitted comments to the FDA public docket and all of you for listening into the today's advisory committee discussions.

This morning, I will present an overview of this Biologics License Application, BLA, and the issues for consideration by the advisory committee. First, I will provide a brief background on ALS and then we'll discuss the clinical development of the product, which I will be referring to as MSC-NTF. I will then summarize the basis for FDA's decision to refuse to file this BLA. Finally, I will go over today's agenda and introduce the questions for discussion and voting by the committee.

The product on their consideration is the master cell or MST-NTF, an autologous product derived from a single bone marrow collection and is composed of mesenchymal, stem and stromal cells cultured under conditions to introduce neurotrophic factor secretion and produce M

MSC-NTF Cells. MSC-NTF is administered intrathecal into the cerebral spinal fluid through a lumbar puncture procedure. The original proposed indication for this BLA was for treatment of a amyotrophic lateral sclerosis, or ALS. However, as it was explained by Dr. Witten, on September 22nd, 2023, the applicant submitted an amendment to the BLA and revised the proposed indication to treatment of mild to moderate ALS.

ALS is a rare, progressive, and fatal neurodegenerative disease. It is characterized by degeneration of upper motor neurons in the motor cortex of the brain and lower motor neurons in the brain stem and spinal cord, resulting in progressive denervation of voluntary muscles. Symptoms typically begin focally, with weakness of a limb or in about one third of patients with difficulty speaking or swallowing. The prevalence of ALS is estimated at 7. 7 per 100, 000 persons in the United States. Therefore, approximately 20, 000 patients with ALS live in the U.S. Around 90 percent of ALS cases are sporadic. And the family history of ALS is present in the remaining 10 percent of affected individuals. The rate of disease progression in patients with ALS is variable. Progressive neuromuscular respiratory failure is the most common cause of loss of life in ALS. The median survival from the time of symptom onset is between three to five years. Sadly, only about 10 percent of patients with ALS live 10 or more years. Although several drugs for ALS have received FDA approval in the recent years, there remains an urgent need to develop safe and effective therapies for ALS.

The MSC-NTF clinical development program consisted of four completed clinical studies. Two single arm, open label, early phase studies conducted outside the U. S., followed by the Phase Two randomized, double-blind, placebo-controlled study, study BCT-001-US, in which 48 patients with ALS were randomized in a three-to-one ratio to either receive a combination of onetime intrathecal administration of MSC-NTF cells together with 24 intramuscular injections

or to receive placebo. The primary endpoint of the Phase Two study was safety. Secondary endpoints evaluated efficacy. The patient's functional status was assessed using the revised ALS functional rating scale, or the ALSFRS-R. The applicant conducted linear regression analysis on the ALSFRS-R results prior to treatment and then on the ALSFRS-R results after treatment. The applicant then compared the linear regression slopes before and after treatment. Finally, one Phase Three randomized, double-blind, placebo-controlled study, study BCT-002-US, enrolled 196 patients with ALS who were randomized in a one-to-one ratio to receive intrathecal injections, one every eight weeks of either MSC-NTF or placebo. The primary efficacy endpoint of Phase Three study was also changed in ALSFRS-R linear regression slope from baseline, that is before treatment, to week 28 after the first treatment. Of note, the Phase Three study is the only controlled study to evaluate MSC-NTF cells using the same route of administration and dosing interval as proposed for the BLA.

This slide summarizes some key regulatory milestones in the development program of MSC-NTF. MSC-NTF was granted orphan drug designation intended to encourage development of drugs for rare diseases and fast track designation, which is designed to facilitate development and review of therapies to treat serious conditions for which there is an unmet medical need. The safety of MSC-NTF had been tested in two early phase studies in Israel before the investigation on new drug, IND, application was submitted to FDA for the Phase Two study to be conducted to be conducted in the U. S. The Phase Two study failed to show a statistically significant benefit of MSC-NTF for treatment of ALS. However, the applicant conducted an exploratory subgroup analysis of rapid progressors versus slow progressors. The applicant defined rapid progress as patients with at least two points declined from screening to baseline in approximately three months in their ALSFRS-R total score. The applicant defined slow progress as patients with less

than two points declined from screening to baseline in their ALSFRS-R total score. FDA communicated to the applicant concerns about the definition of rapid progressors and the exploratory nature of the subgroup findings. However, for the Phase Three study, the applicant then selected only patients who appear to be rapid progressors. Phase Three study also failed to demonstrate a treatment benefit of MSC-NTF on any of the pre-specified primary and secondary efficacy endpoints.

Nevertheless, in September 2022, applicants submitted this BLA based on an exploratory subgroup analysis of the results from the Phase Three study. When a BLA is submitted, FDA expects the application to be complete to permit a meaningful and complete review of the application. Upon receipt of a BLA, FDA first performs a filing assessment to make sure that the BLA contains all the information necessary to permit a substantive review by FDA staff. FDA will file a BLA within 60 days of receipt or will inform the applicant of refusal to file, or RTF. Filing means that FDA has made a threshold determination that the application is sufficiently complete to permit a substantive review. That was not the case for BLA 125782. FDA fully recognizes the urgent, unmet need for additional safe and effective treatments for ALS. Such treatments must meet the critical statutory requirements of substantial evidence of effectiveness, evidence of safety, and demonstration of adequate product quality. But BLA 125782 was scientifically incomplete to demonstrate substantial evidence of effectiveness, and the manufacturing information was grossly deficient to ensure adequate product quality. FDA, therefore, sent the applicant a refuse-to-file letter, which detailed all the deficiencies in the BLA submission and provided FDA's recommendations on how to resolve those deficiencies. I will now go over the issues described in the RTF letter.

The clinical data from the applicant's two randomized, double-blind, placebo-controlled trials did not demonstrate substantial evidence of effectiveness for treatment of ALS. As I mentioned, both clinical trials fail to meet any of their pre-specified efficacy endpoints. This afternoon, my colleagues will discuss the applicant's exploratory subgroup analysis and will explain why such analysis in the setting of a negative study cannot provide evidence of effectiveness.

In addition, the BLA did not contain information on numerous critical elements of product manufacturing, and FDA determined that a substantive review was not possible. The extent of the deficient information, that facilities were not ready to manufacture the product, and the fact that some clinical validation studies had yet to be initiated, suggested that the best path forward would be to submit a new BLA.

Following the RTF letter, FDA and applicant met in January of 2023 to review these deficiencies and to discuss the possible paths forward for the BLA. FDA described the two possible options. The first option was for the applicant to address these clinical and product issues and then submit a new BLA that contains evidence of effectiveness and evidence of safety from new adequate and well-controlled clinical investigations and describe all the necessary validation studies and document that the applicant's commercial manufacturing facilities were ready for inspection. The second option was that the applicant instead could request that the BLA 125782 be filed over protest.

In February 2023, the applicant proceeded with filing the BLA over protest. Following the filing, the applicant also submitted additional exploratory post-hoc subgroup analysis of the clinical data and exploratory analysis of biomarker data and additional CMC information to the

BLA. In addition, five days prior to this advisory committee meeting, the applicant revised the proposed indication for MSC-NTF from treatment of ALS to treatment of mild to moderate ALS.

This morning, following this presentation, our guest and guest speaker, Dr. Evan Snyder will give an overview of cell therapy considerations for the treatment of neurological diseases. It will then be followed by the applicant's presentation. After a short lunch break, we will start with the Open Public Hearing. Afterwards, the BLA review team will give their presentation. And next will be advisory committee discussions, and then their voting and explanation of their votes.

At the end, I would like to highlight the key points that my colleagues will discuss this afternoon in detail. Regarding the MSC-NTF product itself, my CMC colleague will discuss FDA's concerns regarding the lack of sufficient data to demonstrate that product manufacturing is under an adequate state of control and adequate product quality has not been demonstrated. My clinical and biostatistics colleagues will present data from the applicant's two randomized, double-blind, placebo-controlled studies, which both failed to show efficacy, and then we'll discuss the limited survival data for the Phase Three study, which were unfavorable for MSC-NTF treatment group. In addition, my biostatistics colleague will also discuss the applicant's subgroup analysis, and we'll explain why this analysis, either pre-specified or post-hoc, can only be considered exploratory and cannot provide substantial evidence of effectiveness for treatment of either the overall ALS patient population or a subgroup of mild to moderate disease. And finally, my clinical pharmacology colleague will go over the applicant's biomarker data and will show why those results do not indicate a clear association between any assessed biomarker and the clinical benefit to provide supportive evidence of effectiveness.

We are looking forward to the presentations, public comments, and the discussions today. We are specifically seeking the committee's input on the following questions. Please discuss the

data presented in support of effectiveness for treatment of mild to moderate ALS, including consideration of the mechanism of action proposed by the applicant, biomarker data, including neurofilament data, and the clinical data. Please vote on the following question. Do the data presented demonstrate substantial evidence of effectiveness for treatment of mild to moderate ALS? You may vote yes, no, or abstain. If you voted no, please discuss potential designs for a trial to demonstrate substantial evidence of effectiveness for MSC-NTF for treatment of mild to moderate ALS.

And this concludes my presentation. Thank you for your time and attention. Now I will turn the podium back to the chair, Dr. Ahsan. Thank you.

Q & A

Dr. Ahsan: Thank you very much, Dr. Sherafat, for that overview of the BLA. We have five minutes here allocated for questions related to this. This is not meant to start the discussion on the discussion topics or the voting question but clarifying questions for Dr. Sherafat. Are there any questions from the committee? Let's give people an additional moment to raise their hand. I think we are all set. Great, at this point with no questions. Thank you very much. Dr. Sherafat. We'll move on now to the guest speaker presentation on CMC from Dr. Evan Snyder. Dr. Snyder, could you turn on your camera and unmute yourself?

Guest Speaker Presentation on CMC — Dr. Evan Snyder

Dr. Snyder: Okay. Hi, everyone. So, it's an honor to actually be able to present to this committee. As many of you know, I chaired the committee, was on the committee, for many years and I'm actually humbled by the experts that are sitting on the panel now. Any one of them could give this talk. In fact, I already apologized for the fact that I won't be able to do a deep dive because I was asked to pitch this to a pretty broad audience. And also, this is going to be a very personal point of view, because, at least for the first half of my career, I've been following this

and pursuing this pretty assiduously, and many on the committee have been my friends and colleagues throughout this entire journey. So, they'll correct me when I'm wrong, or if I've given it too much of a personal slant.

Anyway, from the very beginning of my career, because I've been both a clinician and a developmental biologist, while pursuing the biology, I've always kept an eye on what the clinical potential could be and what the translational applications could be. So, these are the guiding principles that I began my career with, and I think they still hold true. And as clinicians, when you put on your clinical hat, you often have to make a decision, unlike a basic scientist, with imperfect and incomplete knowledge. Nevertheless, I think there are precepts that I personally held to. The first of course, is if standard-of-care is inadequate or there's no therapy at all. This is the important part. If the data makes sense and they make sense consistent with our knowledge of the stem cell's biology, and the disease pathophysiology and the processes that drive it. And this is obviously a moving target. But I focused heavily on this. And then, of course, if doing what you want to do does not prevent the patient from getting a better proven therapy, for example, using stem cells, if it deprives a patient of radiotherapy, that's not a good idea. If it's safe and does no harm, those are not always the same thing. One can do psychological and financial harm, even if the actual procedure is safe.

So, I don't need to tell this audience that the impact of the stem cell field was that it changed our thinking from a very deterministic point of view in the nervous system, to one of greater plasticity, the notion that there could be adjustments in the brain, in the nervous system, and maybe cells could be the mediator of that.

Nevertheless, stem cells, in my view, serve a teleologic role. They are there to put the system together, so, organogenesis, and then to maintain homeostasis throughout.

And our job, if we want to harness this therapeutically, is to completely understand these processes and respect them and try to harness them and not work at cross purposes to them.

So, what we know is that if there's a graft of a stem cell into a pathologic host, there's a dynamic, both elements change, and they change in response to these various arrows.

And basically, we spend our entire career trying to understand what those arrows are, and I'll go into a little bit more detail over the course of the half hour, but I have to say that probably the greatest unknown as a stem cell biologist, but also a clinician, is completely knowing what needs to be fixed. And this too is a changing landscape, understanding what's going on with the diseases. So, even if we thought we knew what needed to be fixed initially, that changes. And ALS, for example, when I began my career, was purely viewed as a motor neuron disease. And of course, now we know that it's not purely a motor neuron disease.

So basically, even if you have translational aspirations. My view is that you are still a Translational Developmental Biologist.

There’re many ways of getting a neural stem cell nowadays, and they're illustrated here, but at the end of the day, you still need to understand what the biological imperatives of the neural stem cell are.

This is a schematic of its various fates.

But the first is to know the biology of the cell. If you have a stem cell, is it really a stem cell? In other words, candidate here to normal developmental cues, including even in the adult.

So many years ago, we pulled out neural stem cells from a human fetus.

And needed not only to characterize it in the dish, but to show that it could actually participate, for example, in primate development. So, injected into the ventricles of a rhesus monkey, at approximately the same gestational age as what we got the cells from in a human.

And the cells are recognized here as black nuclei, but they migrated up radial glial cells.

And in the purple layer. differentiated into the right cells that's illustrated schematically here. What was interesting is, not only did they integrate into the developing cortex, and the black cell is the donor cell in the cortex between two host cells, but interestingly, they also gave rise to a second population which surround the ventricles, which we now call adult neural stem cells in the secondary subventricular zone.

So, it appeared that the cells not only had the right markers, but they respected the developmental imperatives when in the proper developmental context. So now the question is can they fill a therapeutic gap?

For that, of course, we go to mouse models and rodent models. So again, we needed to do the same kind of exercise to show that these cells could participate in the development of the rodent brain. Now, interestingly, if you put them into the ventricles, which are aligned by the subventricular zone, they will migrate and become various cell types based on the time in development. This is now postnatal.

And what was interesting was, and it's a very simple procedure to do, to go into the ventricles, that the cells, in this case, these are mouse neural stem cells expressing LacZ, which means you can see them as blue cells with an X-gal histochemical stain, spread throughout the brain continuing to express their foreign gene.

Here's a closer view of their intermixed with the host cells. Well, looking at this normal developmental process as a child neurologist,

Made me recognize that expression of a foreign gene throughout the brain was a therapeutic gap, at least back then, for lysosomal storage diseases. This is kids who have a

deletion mutation of a gene encoding for a lysosomal enzyme and the difficulty is that even the smallest amount cannot make it throughout the brain.

We wondered whether just harnessing the normal developmental biology of the cell, whether that could be brought in in a Trojan horse fashion. And early on, we showed that the distribution of the cells, normal cells, wild type cells in a mouse model, in this case, it was MPS VII, could distribute this therapeutic enzyme and eliminate lysosomal storage as you can see in the lower right.

So, this was gene product replacement, but nothing novel other than piggybacking on a normal developmental process with normal cells.

But the same notion also made us wonder, could the same process, just the normal developmental process of the cell, also be used for cell replacement.

And the answer was, one could do this if he, true to the biology, looked at a cell that was born postnatally and had a cell autonomous defect.

Well, the cell type that is present throughout the brain is the oligodendrocyte, and there are diseases in kids in which oligodendrocytes either degenerate or are dysfunctional from the very beginning.

So, the first attempt, of course, was a cell autonomous defect. This is a shiver mouse, which is a myelin basic protein deficient.

And I think as you can see, if we did a newborn injection, you can see why it's called the shiver mouse. This is what an untreated animal does.

This is adulthood, but we treat it at birth. Here's an untreated animal, and then after that, you'll see an animal whose shiver is eliminated.

That is because this was a cell autonomous defect, and one could put in myelin basic protein expressing cells.

Now, a lot of the leukodystrophies are not cell autonomous. In fact, they have a very toxic environment. Krabbe disease, globoid cell leukodystrophy, which is galactosyl ceramidase deficiency, is an example of that. Its defect causes a cytosine toxicity.

Nevertheless, the same approach, to our surprise, was able to be used, in that the cells distributed themselves throughout the brain,

those blue cells, as opposed to the normal animal in which oligodendrocytes by adulthood become absent.

The donor cells could give rise to oligodendrocytes that could myelinate.

The lesson that we learned there, in fact, was contrary to what our expectations were. The younger the cell is, the more resistant it is to a toxic environment, in this case, it was psychosine, if you took the cells and you differentiated them into mature oligodendrocytes, they were toxic. But going into the environment, they were resistant enough to be able to differentiate. And you can increase that resistance if you did some gene genetic engineering.

So, the lesson we took away at that particular point was that neural cell replacement is feasible if the defect is intrinsic to the host cell, and you can distribute it on normal migratory pathways, or it is resistant to whatever the toxic environment is, either based on its natural capability, what engineering you've done, or even its differentiation state.

So, what the lesson here was that you must be aware of what the pathological action is that's ongoing before you want to attempt to treat it.

There could be a range of homeostatic mechanisms. I gave you an example of the diffusible factor, I gave you an example of a cell replacement.

But there are also intercellular communications in development that might also be harnessed. One is cell-cell communication through gap junctions, particularly through Connexin 43.

And what was interesting here is this is a mutant called the nervous animal. And it's Purkinje cells. Here's the normal necklace of Purkinje cells in the Purkinje cell layer, beautiful, so like that. This layer, this necklace, at adulthood, actually begins to degenerate, though the animals are born normally, with a normal Purkinje cell layer.

If we did a transplant, not at adulthood, but day of birth, we had a Purkinje cell even at adulthood.

But the Purkinje cells were not donor-derived. They were host-derived. The donor cells are these green cells, which obviously are not Purkinje cells, that are making cell-cell contact and restoring the metabolism of the endangered Purkinje neuron.

And I won't go into details, but these Purkinje cells die because of an excess of tPA, which is an upstream regulator of a lot of processes central to Purkinje cell function and survival. And what simply happened was that this whole signaling pathway was re-equilibrated by the donor cells through intercellular communication. So that was more balanced.

And that same approach could work in other kinds of Purkinje cell degenerations like spinal cerebellar atrophy type one.

We wondered, could we go extremely early, I was talking about at birth, but a lot of these diseases, at least in kids, we know, begin in utero. Can one go extremely early?

And again, to ask the same question, will the cells participate in normal development?

So, in this case, as we did in the monkeys, but now in the rodent. We injected the cells intraventricularly into the fetus, and in adulthood, and these particular ones happen to be mouse

cells, so you can see them as, as X-gal positive cells, distribute throughout the neural axis, integrate into all the organs that are developing in utero at the time in mid-gestation into the cerebellum, distribute themselves throughout the cortex, intermingle with the host cells. They love to home to blood vessels as many of you know, which is another normal developmental imperative, which could be harnessed.

Of the neural cells, they became astrocytes that participated in blood-brain barrier integrity, became oligodendrocytes in the white matter tracts, and not only became pyramidal neurons, but also non-pyramidal neurons, making synaptic connections onto host pyramidal neurons.

I don't think you can see this very well because it's an EM that simply shows that the donor cells make synapses and importantly receive synapses. So, integrating in there.

And then single-cell electrophysiology simply shows that when they are integrated, they are electrophysiologically active.

And this is a very old study that simply answered the question when they are integrated, can they respond to external cues? And this is an old experiment that Bill Schwartz and I did in which we looked at cells that integrated in the suprachiasmatic nucleus after a mid-gestational transplant.

As you know, the SCN regulates circadian rhythm, particularly in response to light. And what was interesting is that, intermixed with the other cells, when the animal received photic stimulation, that cell, along with the other cells, became active, at least in response to c-Fos activity.

So, knowing that the cells could participate in normal development, we then did the exact same experiment and injected enzyme expressing cells in utero. You can see that function was

sustained on a rotor rod; lifespan was sustained. I think if we had retreated, maybe we could get better.

And the mechanism of actions of the cells were as you might expect. They were enzyme replacement, and the results of that, probably not cell replacement, at least not in the conventional way that we talk about it.

I think it's also, and it might be apropos to this discussion, and again, this is a completely personal view, that the cells will always follow their normal biologic imperatives.

That regardless of the kind of stem cell, and many years ago, I wrote an editorial about a paper that I had edited where it was shown that MSCs from the bone marrow placed into the brain of a mouse model of multiple sclerosis, a very inflammatory environment, the cells did what they normally do. They responded to these inflammatory cytokines, proliferated, and created a connective tissue mass.

So, we've now seen how developmental processes, if they're normal, can be piggybacked upon to complement and cross correct a defect, but now we wondered what happens during a normal injury? What's the normal response of the mammalian brain to an injury? And how did the cells play a role there?

And the injury that again, as a pediatric neurologist, the injury that we looked at was perinatal asphyxia or perinatal hypoxic-ischemic injury, leading to encephalopathy when you focus on the brain. This is a major cause of cerebral palsy. In fact, it's the most common cause of cerebral palsy.

Now the endogenous response. And you can look at the endogenous cells either through BRDU or infecting them with a retrovirus including lacC, is that cells in the subventricular zone, the normal response, should be migrating out to the olfactory bulb. Now, if one imposes an

experimental hypoxic ischemic injury, what we saw is that the cells detoured away from the olfactory bulb, but instead moved to the ischemic region.

And one can see that on the infected side, on the unilaterally ischemic side, the cells would migrate to the ischemic lesion.

When they got there, they did differentiate into neurons, but also differentiated spontaneously, constitutively and to astrocytes and oligodendrocytes and even new immature neural progenitor cells.

There's another way of looking at the data, but focusing on the neurons, they were decorated by synapsin, and again, using the poor man's version of electrophysiology, expressed c-fos, suggesting that they were integrated into networks.

The mechanism is manyfold. Just one of them is that this repulsive molecule Slit-2, which normally pushes cells out to the olfactory bulb, as you can see, on the injured side, redistributed itself, instead pushing the cells up to the ischemic lesion and the attraction, of course, of factors made by microglia and also inflammatory cytokines like SDF1 alpha made by reactive astrocytes and injured vascular endothelial cells.

So, it appeared, kind of an interesting situation, there was an intrinsic self-repair mechanism. However, it might work in mild injuries, but obviously gets overwhelmed in the most extreme injuries. But this was a perfect developmental setting and the developmental recipient using a developmental cell.

So, we then tried to emulate that by using exogenous neural stem cells, I won't go through all the details, except for example, if you place them on the opposite side of the brain, they would migrate to the ischemic region, when they got there, they would populate the area, some of them would actually send processes across to the contralateral side.

But what was most interesting is that, in addition to getting neurons, as we showed with the endogenous cells, there were also glial cells. So yes, new neurogenesis a little bit, but also new oligodendroglio-genesis, new astrogliogenesis, and even new neural stem cells.

Suggesting that the imperative of a stem cell, again, according to its teleologic role, was to try to repopulate this particular area.

Meaning that there's a crosstalk between the neural stem cells, a division of labor, and one of the most powerful mechanisms is when this cell tells this cell, which is not a neuron necessarily, to feedback on to the host or something that. Back then we called the chaperone effect. Nowadays it's called the paracrine effect. But what gets transmitted to the host cell are factors that engender protection, trophic support, detoxification, housekeeping, as I showed with the lysosomal enzymes, blunting inflammation and scarring, mobilizing endogenous cells, and making them send out neurites even pro-angiogenesis in the host. It's accomplished, as I indicated before, by diffusible factors. Those are some of the well-known neurotrophic factors, self-self contact to gap junctions. And now we're starting to appreciate the role of exosomes.

Now, what is interesting is. What, what happens in this particular lesion? The lesion starts off as a dead core, but is surrounded by a restorable penumbra, where, if you do not intervene, there could be problems.

Now, we'd always viewed this lesion as homogeneous. We've developed an MRI technique which can take this homogeneous-looking lesion and, through physics that I won't have time to go into, divide it into a dead, non-rescuable core versus a rescuable penumbra, so that this lesion looks actually like this.

The natural history of the penumbra in this kind of lesion, pseudo colored as blue, is that if there is no intervention, the penumbra, which is near death but not dead, will progress to become core.

But this is a window of opportunity, and if we go into the window of opportunity, as opposed to the progression, if you have two animals that start out the same, and these are now human neural stem cells, if you do nothing, the lesion will progress. But if you intervene, there seems to be a diminution in the lesion.

What seems to be being rescued is the penumbra. The core is not being touched, and that's illustrated over here.

That now the natural history is changed so that now the penumbra returns to normal. The core remains the core. Nothing's going to change that.

This simply is a schematic of what seems to be going on there. Now, why is the penumbra important? Is there anything that happens to be in there? Well, the penumbra's important, not so much what's in there, but what passes through there.

This is a schematic, and you can imagine that if this area is disrupted, here's a schematic over here, that fibers and networks that are global, are disrupted.

Imagine a snowstorm in Chicago. The entire country shuts down.

The mechanism of action is actually a developmental one. We believe that the donor cells not only become trophic astrocytes, but inhibit the normal fate of injured astrocytes to become reactive.

And then there's a whole number of these kind of mechanisms that you're all familiar with, and I won't take time to recount.

What I think is important and relevant to this, however, is the implications. And something that occurred to us, which is rarely done in the regenerative medicine field, and that's to say, who should we not treat? Because their disease is simply not compatible with the known mechanisms of action of the cell. And in this particular case, I would say that a baby who is all core, who has nothing that can be protected, should not be subjected to a neuroprotective therapy. And I think that gets into the ethics, but that's my point of view. And neuroprotection doesn't need to just be cells. It can be all kinds of other drugs that are being tried.

I want to end with the last five minutes with actually showing some of our insights into, into ALS.

As I mentioned, we're starting to recognize that it is a multifaceted complex disease.

You're not meant to read this, but this is what Don Cleveland will often show as to how complex ALS actually is.

It's not just motor neuron degeneration anymore.

Now, how does an animal, in this case we're going to look at the SOD1 mouse, respond to the injury, respond to this degeneration of motor neurons? And again, we look at the endogenous cells to give us some insight.

And it's different than what we saw in hypoxic ischemic injury. Here, the BrdU+ cells, the proliferation are not reparative cells. It's actually mutant astroglia that are, that are toxic to the motor neuron. So here, restoring homeostasis means to suppress that process, perhaps replace it with non-mutant, more trophic astrocytes, and certainly to try to restore the non-toxic environment.

That's something that we approached. This was now about 10 years old. It was a multi-center study with a lot of very well-known people in the ALS field.

This is an example, just a representative example of an animal, an SOD1 mouse, who's doing a rotarod at a time when, when he should actually not have survived. In other words, we saw a delayed disease onset. We slowed the disease progression and improved motor performance.

It was not because motor neurons were replaced.

It was because what we're able to do was inhibit the elaboration of toxic mutant astrocytes, replace them with better trophic, normal, wild type astrocytes and also to produce gray matter oligodendrocytes, which were more protective.

I'll quickly go through these data because I'm running out of time to support that. But about 25 percent of the animals did, and the SOD1 mouse could live longer than a year. And it was not by changing SOD1 mutant expression. Even though we obtained cells, and there was wide migration up and down, consistent with the migratory behavior of neural stem cells that looked like motor neurons. But the key was not the neurons that became but the non-neurons and were able to protect a requisite number of motor neurons. Neuromuscular junctions as assessed by Muni (phonetic) and even respiratory function is as assessed by plethysmography.

The cells expressed many things, including GDNF, and we assayed whether GDNF played a role. The bioassay in this particular case was a spinal cord explant exposed to the cells and showing that there was outgrowth from the ventral horn motor neurons. It could be emulated by GDNF and blocked by GDNF antisense, a GDNF-soluble receptor. Differentiation of the neural stem cells into neurons away from being oligodendrocytes and even an explant from a rat knockout mouse, in other words, that lack of the GDNF receptor.

Not only was there motor neuron preservation, but also a diminution of astrogliosis. In this case, it would have been toxic, a decrease in macrophage and microglial infiltration, and

even a diminution in the internuclear neurofibrillary tangles. And this is simply a meta-analysis to show that the hazard ratio actually favored transplantation. And in fact, the broader the expanse covered by the cells the better the recovery.

Apropos to, I think, what we'll be talking about, the neural stem cells in the intrathecal space, this was intraparenchymal transplants into four cardinal regions that, that mediated life sustaining function. In the intrathecal space, they could make it into the ventral horn if they tracked along the ventral roots, but we've not really explored that in great detail.

Again, in the interest of time, I'll say that the lesson here was that most diseases of the nervous system are actually not a single process, not a single cell type and ALS obviously is a case in point. And for me, one of the appeals of using a cell-based therapy against this is that just the teleologic role, homeostatic role of a stem cell to maintain equilibrium means that it is playing out a number of processes. We have to also, I believe, expand our view of what we mean by cell replacement. It's not just neurons, it's glia, microglia, and the others.

And I think this plays out through not just ALS, but many of the neurodegenerative diseases. This is just a partial list.

So, I'm going to end here by summarizing that in neurologic disease, if one wants to use a neural stem cell to mediate that, there are a number of strategies that can be employed. Cell replacement, I think, is where we began. I think we've become more sophisticated, though there are probably certain situations where that plays a role. And then rescue through many of the different mechanisms illustrated here.

So, I'm going to end now with my principles of stem cell therapy for nervous system disease. Maybe they're shared with other people on the panel. Maybe they're different. I'm certainly open, but this is the result of at least the first half of my career of making many

mistakes. And learning from them. So, I think first, make sure that yourself can participate in normal development, functional processes and homeostatic processes because repair strategies may need to re-invoke developmental strategies. Understand what you are treating. Now, it's much more tractable to protect neural networks than it is to try to reconstruct and replace them. I think three decades of trying to understand developmental biology has taught me at least how difficult that is, much better to protect what was gotten right, perhaps the first time. Of course, that means to treat as early as possible, but then you have to understand how to protect them, which means you have to understand the processes that are ongoing, that if you're going to use the cell, make sure that you're being consistent with the biological imperatives of the organ's own homeostatic system and consistent with the biological imperatives of the stem cell. I would be wary about asking a stem cell to do something that goes counter to those imperatives, unless you have an incredibly deep knowledge of what's tweaking them. Make sure that a cell belongs where you want to put it, because if not, you may miss this key reciprocal crosstalk that I think is key. In fact, it could even become aberrant. Understand the type of pathogenic mechanism. Is it cell autonomous or cell non-autonomous? And that's not just for the cell, but even the product that you want to deliver, can it get to where the action is needed? And when you think about regeneration and neuroprotection, as a neuroscientist, we focus, I think, so much on the nervous system, but for most of these diseases, it's not just neural lineages that are effective. For stroke, trauma, infection, inflammation, it's multiple systems, and in fact, some cell types, including in the nervous system, depend on the health and functioning of non-neural cells. So, with that, I am thankful for your attention. I hope I didn't dumb it down too much, and I'll be happy to take corrections and questions.

Q & A

Dr. Ahsan: Great. Thank you, Dr Snyder. While people get to their raise their hand feature, I want to thank you for your deep and long-sustained impact on the field and you're very nice summary of the potential mechanisms of action, as well as your contribution to this committee when I first rotated on your chair, and you definitely set the standard. So, we have a good number of questions. We have 10 minutes at this point. So, first, I have Dr Fischbeck if you want to go on camera and then unmute yourself, that would be great to pose your question.

Dr. Fischbeck: Sure, it's a nice talk. I like the cartoon at the end. I wonder if you have any thoughts about autologous versus allogenic stem cell treatment? Autologous such as proposed here is using cells derived from the same patient to treat individual patients. And allogenic would be to develop stem cells that could be used one product to treat multiple patients.

Dr. Snyder: Yeah, I mean, that's not a simple answer. It's very complex. And I think it comes down to understanding both the immunology of the host at the particular time you want to intervene and the various processes that are ongoing. What's very interesting is that a true, true stem cell, not just neural, but definitely a neural stem cell, does not have MHC class 2 on its surface. It will develop it, but in its stem cell state will not. So that's that kind of addresses some of the concerns from an immunogenic response. And I would have to say that when all the studies that we've done in newborns have never been under immunosuppression. The reason I'm getting into that is because I know you're getting at the fact that the key to autologous grafts is that they should be immuno-tolerated. And of course, there's an advantage to being able to do that, not the least of which is that if it's an adult you could avoid long term or even prolonged but temporary immunosuppression. I think the answer is I can't give a blanket answer. Off-the-shelf reagents certainly are easier to regulate, easier to manufacture and have much more consistent SOPs and release criteria. So, the goal for me would always be to see, can you do an off-the-

shelf, well-characterized allogenic agent? If the answer is no, then of course you do need to go to an autologous graft, but there as well, the process needs to be exceptionally well regulated with very, very rigid release criteria. The release criteria simply being also that batch after batch, the cells follow and participate in the true mechanism of therapeutic action. I'm not sure if that answered the question, but.

Dr. Fischbeck: That's a good answer. Thank you.

Dr. Ahsan: Thank you, Dr Snyder. We have a host of questions, so maybe we can move through them. Dr. Joseph Wu, could you go on camera and unmute yourself, please?

Dr. Wu: Yeah. Hi, Evan. That was a great talk. Thank you so much. I have a question for you. I think, as you know, for the stem cells, a lot of times it's a numbers game. Numbers games means what is the survival connectiveness of the cells at two weeks, four weeks, two months. So very similar to drugs, PKPD, so, in the neural stem cell field, do you have a sense that if you put in a hundred cells, hypothetically, how many of the cells are still around doing its biological effect at one month, at six months?

Dr. Snyder: Yeah. We've kind of looked at that that over the years and as opposed to some approaches where one is doing a non-neural cell, into a neurologic environment, and the expectation is that the cells will not last. Our hope has always been that that the cells actually will integrate in a benign fashion, continually making whatever product appears to be therapeutic or continuing to do its function. And I think there's some in the Parkinson's field, for example, who do rely on actual integration into circuitry, and if you eliminate those cells with the theory toxin, you actually lose the function. So, our expectation is that we want the cells to survive now, and it appears they do. What we seem to get is pretty robust survival of the cells, not 100%, but maybe anywhere from 20 to 50%, as long as there's a niche for them to exist. If there's not a

niche where they can integrate, then they're not necessary and they die off. What also we've learned is key is particularly when you're talking about using a diffusible factor, let's say in treating a lysosomal storage disease, we've worked out what the ratio of donor cell to host cell that needs to be cross-corrected needs to be, and it's actually a relatively high ratio. It needs to be anywhere from 1 donor cell to 10 to 20 mutant or host cells. Now, if you notice in these Kaplan Meier curves, ultimately, even though the animals lived a number of months, ultimately, they did fall off the cliff. And we think that that happens because ultimately, not because the cells die, we've not really seen cell elimination or cell death once they've been engrafted, but we do think that this is a growing animal, and as the animal grows and the brain grows, it continues to make mutant cells that then surpass our threshold ratio. And the hope then would be, we haven't done this, but then the hope would be to retreat later on. So, the answer is that we don't see a lot of cell death that sometimes in a developing brain, they will be the mutant cells in the animal. They will kind of proliferate and then dwarf the donor cells.

Dr. Wu: Thank you.

Dr. Ahsan: Great. Thanks. Dr. Snyder. Yes, thinking about the cells as a signal and how long they need to persist, whether they act as a trigger or become engrafted within the machinery is very important. Interesting question. Dr. Rajiv Ratan, do you want to go on camera and unmute yourself please?

Dr. Ratan: Yes, thanks. Thanks, Evan. Terrific talk. What are the current best methods for tracking what happens to, for instance, a mesenchymal stem cell in a human, noninvasive?

Dr. Snyder: Yeah, we've had to do this in the brain with the neural stem cells, probably the most effective way to look at cells noninvasively and in real time, longitudinally, would be to co-culture them with a ferromagnetic particle. And it's taken up by the cell fairly benignly and then

do MRI and you can watch the cells in real time longitudinally migrate from their point of implantation to where they ultimately wind up. We've actually used that technique, not only to track cells, but to monitor their degree of proliferation, their speed of migration, and even how long they persist in the brain. And I guess an answer to Joe's question, when we've actually done that with the mouse neural stem cells, in a mouse, we've seen the cells that we've implanted last for more than a year. And some of my initial studies more out of naivete than anything else. The mouse neural stem cells we've done, of course, this involves histology, what I told you about over a year was using MRI, but based on histology, the cells have remained integrated and persistent for over two years in a mouse, but I guess I would do MRI in a human and one could even test that in the road.

Dr. Ratan: Thanks.

Dr. Ahsan: Great. Thank you. Dr. Alexander. Can you go on camera and unmute yourself, please.

Dr. Alexander: Thanks. I was wondering, you made the point that the greatest unknown is what needs to be fixed. And so, I was curious what we know about the evidence that the various neurotrophic factors in question in this application, GDNF, BDNF, VEGF, HGF, GAL1, and LIF are actually deficient in the proximal environs of where there's motor cell degeneration and ALS.

Dr. Snyder: Yeah, that's a great question because the answer to that question is that you know to look under the street lamp, you look for the trophic factors that have either been demonstrated to be more protective. Or that cells make, and there's no question, there's a whole host of factors that we do not know, and we don't need to look at. Experts in ALS can correct me if I'm wrong, but I don't think that we would characterize ALS. as a GDNF-deficient disease or a neurotrophic-deficient disease. I think, again, to get back to my theme, we've been fortunate in that we've

piggybacked upon some of the mechanisms that I like to say nature invokes to try to maintain homeostasis, some of which of the factors you mentioned, and we seized upon them, we've isolated them, we give them exogenously and to some extent they might work, but I don't think that's the heart of the disease. Again, I'm certainly open to somebody who really knows ALS to determine whether they would characterize that disease as, as a trophic-factor deficiency.

Dr. Ahsan: Great. Thank you, Dr. Snyder. It looks like we have no further questions at this point, but there might be the possibility to ask you some questions during the discussion session, so that's great. We are perfectly on time. Thank you so much for being mindful of the time allocation as we have such a busy day. So, at this point, we have built into the agenda, a 10-minute break so we can return let's just make it an even 11:40 if the committee wants to take a few minutes and come back then. Thank you.

BREAK

Dr. Ahsan: Welcome back from the break and we're going to continue our meeting for today. At this point, we're going to hear a series of presentations from the sponsor. I ask that the sponsor speakers introduce the subsequent speaker from the sponsor's team, and I will start the sequence by introducing Dr. Stacey Lindborg, who is Co-Chief Executive Officer of Brainstorm Cell Therapeutics.

Applicant Presentation

Introduction — Dr. Stacy Lindborg

Dr. Lindborg: Good morning. Thank you. I want to thank the FDA, the Chair, and members of the panel for the opportunity to present our new cell therapy, NurOwn, for ALS. I also want to thank all of the people that participated in our trial and the thousands more living with ALS for your persistence and commitment to finding needed therapies for this relentlessly progressive fatal illness to that end I recognize that another advisory committee has met several times over

the past 12 months to discuss two ALS drug candidates in which regulatory flexibility led to both drugs being approved. All are important discussions. As you'll hear today, there remains acute unmet need. Therefore, we don't just need one or two more drugs, we need an arsenal of effective therapies for people living with ALS.

Before getting started, let me take a step back and frame for you why we are here today. When the trial originally read out, the most straightforward decision for the company was to walk away from ALS. In fact, like the FDA, we originally looked at this as a failed trial, but when we delved more deeply into the pre-specified subgroup of 35 and above, we saw that more participants with NurOwn compared to placebo have a large clinical response and two points of function preserved across the NurOwn treatment arm, both of which are highly clinically meaningful. And what struck us most is that this is exactly what we expected to observe. We'll show you later in the presentation that these results are not by chance but are a direct effect of NurOwn. And then the biomarker results came in, and this caused us to look even closer at the data. The most illogical thing we saw was that a clinical response on placebo in the most advanced patients was what was occurring. When we looked further into this, we uncovered an inherent mathematical floor effect of the scale that was skewing the data. So, with all of this in mind, the results in the pre-specified subgroup, the biomarker data, and the floor effect, we felt strongly we needed to bring this forward for patients. This is ultimately why, in response to the refuse-to-file letter, we ask the FDA to discuss the validity of this data in this public forum.

Before I continue, I want to take a brief moment to address CMC concerns raised in the refusal-to-file letter, which were referenced in FDA's briefing book. Brainstorm has made progress on some items and started studies to address others. The dose defined in Phase Two, Phase Three, and in the CMC release criteria was a range 100 to 125 million cells, which we

consistently produced batches of product that are within this range and all participants in both late-phase trials were dosed within this range. The production process for NurOwn is both robust and consistent. All products manufactured to date have passed the pre specified criteria for release with approximately 500 products manufactured for around 200 individuals. NurOwn is a unique product with a unique manufacturing process. In fact, it would be the first cell therapy for a neurodegenerative disease, if approved. It's well known that each individual cells are unique and can be influenced by genetic, epigenetic, developmental, and environmental factors. Reproducible production was done that met specification. Finally, we acknowledge that additional work needs to be done and to be completed to fully satisfy FDA requirements. We will continue to work with FDA to ensure cell manufacturing meets all FDA requirements and specifications and we're confident in our ability to do so.

FDA has described the importance of exercising regulatory flexibility for life-threatening and severely debilitating illnesses, including its guidance specifically dedicated to ALS. They note it is appropriate to exercise the broadest flexibility in applying the statutory standards in this setting while preserving appropriate guarantees for safety and effectiveness. FDA leadership has further underscored the importance of this approach for people living with ALS and has done so in its guidance in addition to through actions through recent approvals. It's noted in the ALS guidance that an objective finding, even if of relatively small magnitude, may contribute to the assessment of benefits and risk. FDA's regulatory flexibility for ALS supply is important context for the discussion today, and we hope you will keep it in mind in your deliberations.

Now let me tell you about NurOwn. NurOwn is a novel, innovative, cell therapeutic approach to treating ALS. NurOwn leverages cell culture methods to induce autologous bone-marrow-derived mesenchymal stem cells to secrete high levels of levels of neurotrophic factors

to modulate neuroinflammatory and neurodegenerative disease processes, which promote neuronal survival and improves neurological function.

Importantly, NurOwn was designed to minimize the risk of an adverse reaction. The autologous cells are recognized by one's body as the individual cells, avoiding an unwanted immune response. In addition, the manufacturing process is free of antibiotics and Xeno-derived proteins and does not include genetic modifications or use viral vectors.

NurOwn is designed to effectively and simultaneously deliver multiple neurotrophic factors and immunomodulatory molecules in close proximity to the site of damage for people living with ALS. Neurodegenerative diseases including ALS are known to be deficient in neurotrophic factors and to have increased inflammation. In an ALS mouse model, mesenchymal stem cell treatment was shown to delay motor neuron degeneration to improve motor performance and prolong survival. In preclinical studies evaluating direct CNS administration of NurOwn, in animal models of ALS and in other neurodegenerative diseases, have consistently demonstrated neuroprotective effects of NurOwn. These combined findings make a neurotrophic-secreting mesenchymal stem cell treatment an excellent therapeutic candidate for ALS. And in our clinical trials, we found consistent findings with biomarker data.

The clinical program supporting efficacy and safety for NurOwn includes data from a robust preclinical program and four clinical trials. For today's presentation, we'll focus on results from our pivotal Phase Three study. The FDA granted NurOwn orphan drug designation in 2011 as well as fast track designation in 2014 for the treatment of ALS. During the Phase Three trial, it became clear the FDA preferred our key secondary endpoint, which was the average change in the ALSFRS-R, and which we'll be discussing at length, is a scale that measures function. They had a preference that this serves as the primary endpoint, citing ease of interpretation of the

clinical meaningfulness. We proposed amending the protocol to make this the primary endpoint. However, the FDA advised against an amendment. The FDA emphasized it was committed to looking at the totality of evidence from our Phase Three study, which, in their words, had been reasonably designed to collect the important data relevant to an evaluation of efficacy. Thus, our BLA was filed last year. Importantly, we're planning an additional randomized and controlled study, which will have an open-label extension to evaluate the long-term impact of NurOwn.

This Phase Four trial design was generated with insights from our Phase Three trial, along with input from a scientific and patient advisory board. We have a near-final protocol, and we'll finalize the design in order to enroll participants in the first half of 2024. The trial will be a robust, multinational trial designed to provide additional evidence of the efficacy and safety of NurOwn. The study will allow for treatments with the current standard-of-care in both arms. Let me now highlight a few points about our Phase Three trial.

Our Phase Three trial enrolled a cohort of participants with advanced ALS, approximately 25 percent based on their ALS functional baseline score. This graph shows the average scores of participants in recent large ALS clinical trials. Please note that the recently approved ALS drugs are shown in light blue. The NurOwn population at the bottom is clearly an outlier, with baseline values in the study ranging from 16 to 46. There was a desire from the principal investigators to extend the inclusion criteria to include a broader set of trial participants. This resulted in a unique and atypical trial population that is also more representative of the broader patient population. As we analyzed our Phase Three data, we recognized that this unusually large cohort of participants with advanced ALS was uncovering an inherent floor effect in the ALSFRS-R scale, which was impacting the data. The FDA has recently recognized the floor effect at a conceptual level and comments that it can occur either at an item level or at an overall scale score level, and results in

the inability to capture progression at the bottom of the scale. The study had a pre-specified subgroup based on the threshold of 35 on the ALS functional rating scale. The baseline average for participants in this pre-specified subgroup is 38, as noted by the green star, which is much more in line with these recent ALS trials.

Today, you will hear that ALS is a universally fatal neurodegenerative disease with a critical unmet need. The endpoints, all of which are valid measures important to ALS, did not reach significance. However, NurOwn did reach nominal significance and produced a consistent clinically meaningful treatment effect on an important pre-specified subgroup of participants with baseline scores 35 and above. Additionally, results in participants with no floor effect at Baseline further support these findings. You'll see biomarker results across all trial participants that further support the clinical benefit and mechanism of action of neuron. Importantly, the biomarker data you will see is in a set of biomarkers that are highly relevant to ALS disease with an association to clinical outcomes clearly established in the literature. And lastly, our data support the safety of repeat intrathecal administration confirming the positive benefit risk of NurOwn.

The proposed indication for NurOwn is the treatment of mild to moderate ALS as this is where we observe strong evidence for NurOwn as a safe and efficacious treatment for ALS from Phase Three. We also are seeing supportive evidence across all patients.

Here's the agenda for the rest of our presentation.

We also have additional responders with us here today to help address your questions. Thank you. And I will now turn the presentation over to Dr. Windebank.

Introduction: ALS Landscape and Unmet Need — Dr. Anthony J. Windebank

Dr. Windebank: Thank you very much. And good morning. I'm Tony Windebank, the Professor of Neurology and the Judith and Jean Pape Adams Professor of Neuroscience at Mayo

Clinic. I've been treating people with ALS for more than 40 years and have been Principal Investigator in many clinical trials for neuromuscular disease, including ALS. I'm here today to provide some background on ALS, but I'm excited to present this data. It's a miserable disease. The few options we have available and importantly, the need for more treatments, that target different aspects of this universally fatal heterogeneous disease. By way of disclosure, I am being reimbursed for my travel, but not being compensated for my time in preparing for today's meeting.

As very nicely described by Dr. Sherafat, amyotrophic lateral sclerosis is a devastating and progressive neurodegenerative disease that results in dysfunction and death of motor neurons in the brain and spinal cord. The motor neurons predominantly affected in ALS are those that initiate and control voluntary movements. When the neurons become damaged, and eventually die, brain can no longer control muscle actions.

This results in rapid loss of basic function and ultimately death in all people with ALS. With a progressive loss of voluntary muscle action, people with ALS lose their ability to speak, eat, move, and eventually breathe. And as pointed out, people with ALS have a median survival of two to five years from symptom onset. And even with the recent approvals, we still have too few treatment options for people living with ALS.

The biological mechanisms of ALS are complex, and I think Dr. Snyder gave just a beautiful description of the complexity underlying ALS and the possible potential role in the future for neural progenitor cells, but also demonstrated that a multifaceted approach, depending on our present understanding of the complex mechanism may be the way to move forward. The current scientific evidence indicates that neurodegeneration may be linked to deficient neuroprotection and neuroinflammation. Of the current investigational therapies, stem cell

treatment has the potential to synergistically tackle these interrelated pathomechanisms. Another beneficial effect of MSCs is related to their intrinsic capacity for immunomodulation, which is especially relevant considering the growing evidence for the role of inflammation in ALS, pathogenesis, and progression.

The ALS functional rating score is the primary tool for capturing ALS disease progression, clinical practice, and in clinical trials. The scale evaluates the level of impairment of patients with ALS in twelve functional activities, and each activity is rated from zero to four. The score of four is normal function and zero is the worst. The scale is bounded between zero and four, meaning it cannot measure below or above. These twelve functional areas further group into four domains that encompass bulbar, fine motor tasks, gross motor, respiratory function.

Now importantly, every point on the scale matters. A one-point increase can mean improved physical function and quality of life for people living with ALS. Examples of one-point differences on the scale include the ability to turn in bed without assistance, requiring a wheelchair versus walking with assistance, the ability of a patient to still feed themselves, and independence to dress oneself.

Conversely, each point reduction on the ALSFRS scale results in a decline in function and quality of life. In fact, the research has shown that a one-point reduction is accompanied by a seven percent decline in quality of life. While the ALSFRS is the most effectively, most widely used tool available to measure disease progression, its utility in clinical trials is hampered by its limited ability to measure changes in physical function in those with higher and lower functional status, particularly in the study duration of ALS trials, which must be limited for ethical reasons. Thus, this ALSFRS scale shares with every bounded rating scale the challenge of a floor and ceiling effect.

Biomarkers of disease progression and underlying disease mechanisms are starting to emerge. And while the field is early, there are a number of biomarkers associated with neurodegeneration, neuroinflammation, and neuroprotection that correlate with disease severity. Of all the emerging biomarkers being studied in ALS, we know the most about neurofilament, a marker of motor neuron integrity, shown to be elevated in CSF in patients with ALS, and to correlate with rate of disease progression.

To summarize, the field is growing, which is exciting for me, my colleagues, and importantly for people with ALS. But we still have too few options to help manage this relentlessly progressive heterogeneous disease, highlighting the significant unmet need for more and clinically meaningful treatments that will slow the progression of ALS. I've been involved in dozens of clinical trials for serious life-threatening disorders such as ALS. It is a complex and difficult disease to study. So, when we see results that are promising and will make the difference in patients' lives, as is the case here, we do our best to ensure that patients have access as rapidly as possible. We can't afford to dismiss the possible treatment, even if it only helps a subset of people. Thank you. And I will now turn the presentation back to Dr. Lindborg.

Efficacy / Phase 3 Results — Dr. Stacy Lindborg

Dr. Lindborg: Thank you, Dr. Windebank. Today, I will review the efficacy results from our Phase Three study showing a consistent, clinically-meaningful treatment effect across pre-specified clinical endpoints in a pre-specified subgroup, which is further supported by clinical evidence in post hoc subgroups and in biomarker evidence in all trial participants.

The Phase Three study, BCT-002, was thoughtfully designed by Brainstorm in collaboration with some of the most respected academic neurologists dedicated to ALS drug development. This trial followed a Phase Two study where there was stronger efficacy in a pre-specified group of fast progressors compared to slower progressors. The intent of the Phase

Three study was to observe enough decline in participants such that a treatment effect could be adequately assessed in the trial. The study was conducted at six sites in the U. S. and was comprised of a 20-week pretreatment period, a 16-week treatment, and a 12-week, post-treatment follow-up period. Participants were randomized one to one in either NurOwn or placebo. Safety data beyond week 28 were reported by principal investigators in the safety database for approximately five percent of participants. All data in the safety database is included in our safety analyses. Three doses were administered in the trial intrathecally at two months, two months apart at week zero, week eight, and week 16. Of the 196 participants who were randomized, 189 received at least one treatment and 145, or 77 percent, completed the trial, which is impressive, especially given that the study was run during a global pandemic. As the study progressed through the pandemic, hospital policy required nonintervention visits to be converted to remote visits. This resulted in CSF samples and participants later in the trial being missing. In the 98 percent of participants who contributed samples, we observed over 75 percent of the samples that were intended to be collected. The visit with the greatest impact was visit 20, but with over three quarters of the samples per the protocol collected, the data set remains an incredibly robust, longitudinal data set that which we can learn from.

The primary endpoint was a responder analysis and clinical response was defined as a decline in the rate of disease progression in the post treatment period by 1.25 points per month or more compared to the pretreatment rate of decline, which for some participants meant the observation of an improvement in ALSFRS-R scores. Our key secondary endpoint was the ALSFRS-R change from baseline. The study also included other secondary endpoints, which are shown here. As noted earlier, there was one efficacy subgroup that was pre-specified in advance

of the database lock and was based on the baseline ALS functional grading score threshold of 35 or greater. Let me show you an illustration of our primary endpoint.

This data on this slide is a participant from the Phase Three trial of a person treated with NurOwn. This participant met the criteria for clinical response for the primary endpoint. Prior to treatment, the rate of decline in this individual was negative 1.4 points per month, which slowed during the treatment period by 1. 52 points per month. Which is more than the response definition of 1. 25 points per month. And as you can see, there's a stable trajectory in the treatment period with a slope that is positive and near zero, or a slight increase in scores over time. What's important is that this criterion is a substantial bar for clinical response.

The trial enrolled a set of participants with a broad range of disease severity. The trial was focused on removing participants unlikely to decline in the trial, along with those unlikely to be alive at week 28. Within the study, baseline disease characteristics were well balanced between the treatment arms in all trial participants. The trial enrolled more people with advanced ALS disease, including approximately 25 percent of participants with the baseline value of 25 or below, a sample much larger than anticipated. The average time since diagnosis was 6. 5 months and 19 months since symptom onset. And consistent with standard-of-care, about 65 percent of participants were on riluzole when they entered the study.

Baseline disease characteristics were also balanced across treatments in the pre specified subgroup of those with baseline scores 35 or higher. The only exception was a higher rate of riluzole use in the NurOwn-treated participants at baseline, a finding that was carefully explored and did not influence clinical outcomes.

The primary and secondary endpoints in all trial participants showed small differences between treatments that were not statistically significant. The Kaplan Meier estimates for event-

free survival due to disease progression or any cause are similar across treatment groups at week 32, which is true in all participants and in the pre-specified subgroup. This analysis appropriately includes all data in the safety database as provided by the principal investigators at each of the sites. For purpose of comparison to the data reported by FDA, we report event-free probability from the Kaplan Meier curve. The p-values for survival analysis is from a pre-specified Cox proportional hazard model adjusting for baseline coherence, which is appropriate given the heterogeneity in this patient population.

The pre-specified subgroup of participants with ALSFRS-R scores 35 and above is highlighted in the light blue circle here relative to the size of the total participants in the trial. This subgroup had 31 percent of participants, with 26 participants randomized to NurOwn and 32 randomized to placebo.

NurOwn demonstrated a large and clinically meaningful treatment difference on the primary endpoint with a 19 percent higher response rate with NurOwn compared to placebo, which was not significant. On the key secondary endpoint, NurOwn treated participants had on average,2.1 points of function preserved across the trial compared to placebo with a nominal p-value of the 0. 050, even with a small sample size, we have a nominal p value of 0. 050. For the remainder of this presentation, all p-values will be reported as nominal.

In the subgroup of participants below the threshold of 35, the rate of response and the average change from baseline in ALSFRS-R was similar between treatments.

Similar to the primary and the key secondary endpoints, the results across the secondary endpoints become larger, favoring NurOwn in the pre specified subgroup of participants with less advanced disease.

Estimates for the event-free probability for death due to disease progression or due to any cause were rare, and in the pre-specified subgroup, given the low event rate, were unable to be compared statistically.

Starting with the primary endpoint, this slide focuses on an important perspective, which is the treatment effect observed over time in participants with the pre-specified subgroup. The higher rate of response with NurOwn participants observed at the end of the trial was consistent across the entire trial, starting as early as week two, the first post-treatment time where the ALS functional rating scale was measured. And this is true at every other time point where the scale was measured across the trial.

Likewise, the average change from baseline across each time point in the ALSFRS-R assessment, again, illustrates separation between treatment groups in this pre-specified subgroup. As we can see after the second dose, NurOwn participants lose less function, and a two-point difference of function is maintained through the end of the trial, which I think we can all agree is a clinically meaningful difference for people living with ALS.

The consistency of treatment effect in this subgroup is also observed in the subdomains of the ALSFRS-R scale. We can see through this slide that the treatment effect with NurOwn is driven by more than one subscale. In other words, there was less decline in function in the NurOwn arm relative to placebo in the total score, in addition to the subscales. I'll now turn the discussion over to Professor LJ Wei to present methodology he has developed, which we'll use to assess the NurOwn Phase Three data.

Totality of Evidence in Prespecified ALSFRS-R ≥ 35 Subgroup — Dr. Lee-Jen Wei

Dr. Wei: Thank you, and good morning, and also good afternoon. I'm LJ Wei, a Professor of Biostatistics at Harvard University. I have been doing clinical trial methodology research and also heavily involved in conducting clinical studies for the past 40 years. Quite a few of my

proposed analytical methods for designing, monitoring, and analyzing clinical studies have often been utilized in practice. I'm being compensated for my time in preparing for today's meeting. In her presentation, Dr. Lindborg presented the results from a pre specified subgroup of patients with a baseline value greater or equal to 35, suggesting that there were clinically meaningful treatment effects based on the primary and the key secondary endpoint. Although the sample size for this subgroup is only one third of the total trial size, 26 traded and 32 controls, we can see a clear trend for a positive retrieval factor. Here allow me to spend a few minutes to discuss the totality and the consistency of nuanced treatment benefits for this particular subgroup from various angles and also from different perspectives to assess whether the treatment effects are real.

A few years ago, there was a conference held in Washington DC, which was sponsored by the US FDA and the Duke University to discuss how we could speed up the evaluation process of new experimental therapies for real diseases. At the end of the conference, one take home message was that for clinical studies of real diseases with a rather heterogeneous patient populations, the standard analysis aiming at a single summary endpoint may not be ideal or efficient for assessing the treatment, clinically and statistically. I may also like to make a note: in that conference, the FDA and attendants also agree we should be more flexible interpret a key value. In the NurOwn study, for each patient, multiple outcomes are collected which reflect on what is this burden and the progression evaluate from various angles and the perspectives. The question is how to utilize multiple outcomes to assess a global treatment effect beyond using endpoints at only one time point for decision making. Using this approach allowed us to explore how robust and consistent the data are in this particular pre-specified sample, which may ease the concern that the observed treatment effect is just a spurious finding.

Instead of using the outcomes only at week 28, we consider the temporal treatment effect profiles as shown on the screen. On the top left-hand side is the curve connecting the response rates observed at a set of pre-specified time points. The higher the curve, the better the study's therapy. The NurOwn curve in blue is uniformly above placebo in gray. At a very early time point, the separations of these two curves are consistent over time on the response rates. It's about a 19 to 20 percent differences between the two curves. On the right upper panel are the curves for the changes of ALS scores over time. Again, the treatment differences were observed after week 8 and sustained over the entire study period. The same patterns are observed across the other two clinical endpoints, especially for CAFs, which is a outcome combining patient function and survival together. In the briefing document from the FDA, this was cited as an important endpoint for ALS studies. For this plot, there's an impressive separation between two curves favoring NurOwn. Now, the question is how to quantify such positive profiles over time, also across the four clinical outcomes, simultaneously. To this end, we utilize a simple statistical procedure by combining standardized treatment estimates, which is simply the treatment effect divided by its standard error estimate, the so-called Z-score. If there were no differences between treatment and control, the chance of observing these positive patterns from four outcomes is only 2.1%, a quite a small value. This quantification suggests a positive global training effect in a much broader sense compared with a fixed time analysis with a single outcome. This method was proposed back in 1984 by my colleague, Professor John Martini, and myself, which has been utilized often, combining information from multiple outcomes, quantitatively, especially for real diseases, and clinical studies. The details are given in the sponsor's briefing document.

Let's look at analysis of ALS's a functional rating scale by exploring four subdomains. Instead of focusing on the total score, we can look at the individual 12 items grouped by four

categories. Now, in the screen, we see the curves were constructed based on the individual category specific scores. In all categories, except for the gross motor, the NurOwn blue curves are always above the gray curve. This suggests NurOwn appears to be effective, again, in a much broader sense than using a single total score analysis. To quantify statistically how this global profile is real or just by chance, again, we combine the standardized group differences, which is on this course, over an entire study period. The p-value is 4.5 percent for observing this pattern. This means if there were no treatment differences, the chance of observing those positive profiles will be very small.

To close, we observe a consistent, robust treatment effect in this pre-specified subgroup of less advanced patients. Based on the above analysis, the observed treatment benefits are likely driven by the true treatment effects, but not the spurious findings. Of note, the positive treatment effects have also been observed across other subgroups, including a subgroup threshold defined a median of the baseline ALS score, which is 32. We notice the statistical evidence becomes stronger when the sample size is getting larger. To illustrate this phenomenon, additional analysis will be presented by Dr. Staff. And Dr. Bowser with a larger subgroup consisting of less advanced patients defined by different criteria. I thank you, and I will now turn to presentation over to Dr. Staff.

Supportive Clinical Evidence — Dr. Nathan Staff

Dr. Staff: Good morning, I'm Nathan Staff, Professor and Vice Chair for Research in the Department of Neurology at the Mayo Clinic. As Dr. Wei mentioned, I would like to walk through some additional supportive clinical evidence by sharing data from a larger post hoc subgroup from NurOwn's Phase Three data. These are also participants earlier in their disease course. I will also describe the challenge that the ALSFRS-R scale brings into the analyses that include participants with advanced ALS disease. I am not being reimbursed for my travel or

being compensated for my time in preparing for today's meeting. I was an investigator on the NurOwn Phase Two and Phase Three clinical trials.

Earlier, we showed you FDA's definition of the floor effect. This is an example of what the FDA referred to as a total score floor effect and shows how participants with advanced ALS have high susceptibility of being misclassified as being a responder on the primary endpoint. This participant, who was randomized to placebo, had a baseline ALSFRS-R of 23, and they already had zeros on three of the scales item scores. During the treatment phase, this participant demonstrated plateauing on the ALSFRS-R scale, ultimately reaching zeros on seven item scores, five of six fine and gross motor items, and two of three respiratory items. This placebo participant is considered a responder on the primary endpoint and is an example of a misclassification due to the floor effect. This is an exact example of what the FDA has described as a total score floor effect.

In the ALSFRS-R scale, when a given item reaches zero, no further decline can be measured in that domain by the scale, but it is important to recognize the participant's weakness may continue to worsen or plateau. Furthermore, in ALS clinical trials, not all aspects of the scale are equivalent. The fine and gross motor domains have been estimated to encompass 70% of decline in the scale during clinical trials. There is less contribution from bulbar and respiratory domains due to the standard ALS clinical trial inclusion criteria. When we look at the different ALSFRS-R domains in the NurOwn Phase Three trial, the participants with advanced ALS had a high rate of zeros in items within the fine motor and gross motor subscales, which averaged 40 percent of those items. This high percentage of zeros in those domains that tend to most decline during clinical trials further confounds the ability to detect changes in these participants.

As shown previously, the low baseline ALSFRS-R scores in the NurOwn Phase Three trial is really an outlier when compared with other ALS clinical trials, as well as with PRO-ACT, which is a large database of clinical patient records from ALS Phase Two and Phase Three clinical trials. Interestingly, within the PRO-ACT database, a plateau due to the floor effect is actually seen in about five percent of the participants, compared with a much greater 22 percent of those who received placebo in the NurOwn Phase Three trial, using the same analysis. While the floor effect has not been discussed in the ALS literature until recently, it is in fact present even in these historical trials, just not to the degree it has been seen in the NurOwn Phase Three trial. It is likely that the floor effect hasn't been discussed as a phenomenon because in any one trial, the number of people impacted is small relative to the trial. It just hasn't been visible in those other trials.

In the NurOwn Phase Three study, we see that the floor effect became more prominent in those with lower baseline ALSFRS-R scores. In this graph, the blue bars show the percentage of all participants in the NurOwn Phase Three trial that have at least one item of zero at baseline. These percentages are then binned at each baseline score. Note that 100 percent of people with a score of 24 and below had at least one zero at baseline. We will use these criteria to define a post hoc subgroup of participants with no evidence of an item level floor effect at baseline. In other words, a subgroup of those participants in the yellow bars.

This subgroup has a mean baseline score of 35, shown here with the green star, which again puts it in closer line to the typical population that has been studied in recent ALS clinical trials.

Now the agency contends that no floor effect was observed in this study. And they use this figure from their briefing document as their primary evidence. The top two solid lines are

participants with no item level floor effect. NurOwn is in blue. Placebo is in red. The bottom dotted lines are the participants that have an item level floor effect at baseline. That is, participants with one or more items of zero at baseline. The FDA concludes that because NurOwn is declining more than placebo, there is no floor effect. However, we contend that this conclusion is flawed, and let me explain. Overall, there were 46 participants in the NurOwn arm, and 37 with placebo, who were classified as having an item level floor effect at baseline. But when we look carefully at this data, we see that while there were fewer participants that were placebo in this group overall, importantly, there were more than 2.5 times the percentage of placebo participants who demonstrated a plateau on the scale, specifically 24 percent with placebo compared to only nine percent with NurOwn. This is important because that larger cohort of placebo participants that plateaued would, by definition, not be able to drop their score from baseline, as the scale is unable to measure further decline in that item. This problem with the floor effect in the ALSFRS-R scale means that the larger decline in NurOwn-treated participants in this group is primarily a mathematical artifact due to the imbalance of participants with plateaus. This not only highlights the relevance of removing the data from the analysis, but really mandates that we do so.

Now, let's turn to the data in participants where we can confidently estimate the treatment effect. As you can see, the pre-specified subgroup with an FRS-R score of 35 or greater is a subset of the much larger group that does not exhibit any item level floor effect at baseline. This subgroup, without an item level floor effect, collectively makes up more than half of the trial participants.

On the left of the graph, are the primary and key secondary endpoint results for those in the subgroup of a baseline ALSFRS-R 35 and higher that Dr. Lindborg showed you earlier. Now

on the right are the same results in this larger cohort of participants that exhibit no item level floor effect at baseline. As you can see, we observed consistent results in both the primary and key secondary endpoints across both groups. Clinically important treatment differences are observed on the primary outcome of a 19 and 18 percent difference respectively, with a 2.1- and 2.3-point difference on the key secondary outcome, with nominal p-values of 0.035 and 0. 04 respectively in this no floor effect subgroup.

And when we look at the secondary endpoints in this subgroup, we see similar results as to those shown in the 35 and above pre-specified subgroup. All results across these secondary endpoints favor NurOwn.

When we look in this subgroup at the totality of evidence, as described by Dr. Wei, we see consistent and sustainable improvements with NurOwn on the primary and key secondary endpoints. There is about a 20 percent difference between the two curves on both graphs. And to quantify statistically if this is real or just by chance, we combine the standardized score differences, or Z-scores, over the entire study period. The one-sided p-value on the primary endpoint is 0. 005 and 0.007 on the secondary, suggesting that the observed differences between the two groups would be very unlikely if there were no treatment differences between these two arcs.

And we see similar results when looking at the totality of evidence in participants with no item level floor effect across the different FRS subscales, where there's a p value of 0. 007 for observing this pattern from all four subscales. In other words, if there was no treatment difference, then the chance of observing this pattern would be very unlikely.

In summary, the floor effect observed in the NurOwn study was real, must be accounted for, and further supports the efficacy observed in the baseline of 35 or greater pre-specified

subgroup. Almost half of the participants had at least one item starting at zero, and a high rate of participants also plateaued at a total score, which contributed to misclassification of the responders in the primary endpoint. It also made it impossible to confidently detect overall worsening of function in the endpoints for participants impacted by the floor. When analyzing the primary and secondary endpoints in those participants that had no item level floor effect at baseline, there were clinically meaningful treatment effects with NurOwn, and these effects exhibited nominal significance pylon points. Finally, the totality of evidence further supports the validity of the data, and that these results did not occur by chance. Thank you, and I'll now turn over the podium to Dr. Bob Bowser.

Supportive Biomarker Evidence — Dr. Robert Bowser

Dr. Bowser: Thank you, and good morning or good afternoon, depending on where you're located. I'm Bob Bowser, the Chief Scientific Officer, Professor, and Chair in the Department of Translational Neuroscience at the Barrow Neurological Institute in Phoenix, Arizona. I've worked on discovering and validating biomarkers for ALS for more than 25 years and more recently measured various biomarkers in patient-derived samples from multiple ALS clinical trials. I am being reimbursed for my travel but not compensated for my time for today's meeting. Today I'll review the biomarker data from the Phase Three study, which further reinforces the clinical conclusions.

Recall this list of emerging biomarkers that Dr. Windebank showed earlier. We select three biomarkers from this list, which we'll highlight today. These were chosen to focus due to the fact that they were being identified as being predictive of clinical outcomes in the trial through a pre-specified statistical model. Those biomarkers were Neurofilament Light Chain, TGF- β1, and Galectin-1. And for completeness, we've included a pro inflammatory biomarker, MCP1, as its role as a biomarker and its importance in ALS is well established. Before we look

at individual biomarker trajectories, let's review the biomarkers by pathway, where a significant treatment improvement was observed with NurOwn compared to placebo.

CSF was collected across the trial at seven distinct time points from baseline, which is pretreatment, to 20 weeks following the first dose. Overall, 33 biomarkers were analyzed across three key pathways. This represents one of the largest biomarker studies performed in an ALS clinical trial. The biomarker study in this trial was carefully planned and included a second analysis plan for the trial focused on biomarker data signed off in advance of the database lock. The total number of biomarkers evaluated in each pathway are shown on the right and those listed had significant treatment induced differences in data from all participants in the trial, and favoring NurOwn compared to placebo. Multiple biomarkers on this slide have been widely studied and published for their relevance in ALS, covering three important pathways relevant to the pathophysiology of ALS. That is neurodegeneration, neuroinflammation, and neuroprotection. The biomarkers on this list offer a lot of excitement for the potential biological impact of NurOwn. Included in this list of biomarkers of interest in neurofilament light chain which has been widely published in neurodegenerative diseases, including ALS. For many others, there's a rich literature suggesting the role in the disease process.

NfL is an important neurodegenerative biomarker that's gained even greater interest in ALS through the recent review and approval of an ALS product, targeting people living with an SOD1 mutation. Treatment-induced reductions in neurofilament light chain was a basis for accelerated approval. And it was believed that reductions in plasma NfL were reasonably likely to predict clinical benefit in ALS. In this trial, we observe NfL levels initially increase in NurOwn-treated participants, followed by a steady decline throughout the course of the trial. This graph summarizes all participants in the trial. Treatment curves separate following four

weeks and ultimately reach, on average, an 11 percent reduction from baseline at week 20 with NurOwn treatment. Placebo values remain stable relative to the baseline at the end of the study. The treatment differences in percent reduction of the NfL to baseline, or from baseline to Week 20, was significant at the PA (phonetic) less than 0.05 level. As noted, on the prior slide, we observed significant treatment differences in other neurodegenerative biomarkers, some with rapid onset of difference, such as death receptor 6, with a reduction from baseline in neuron treatment participants of 51 percent in week two, and others with a very similar pattern to NfL, such as phosphorylated neurofilament heavy chain which was reduced by 13 percent from baseline at the end of the study. Now let's look at the other select biomarkers from the other pathway.

The panel on the left shows levels of TGF- β1, an anti-inflammatory biomarker in all participants, with increased levels in the NurOwn-treated group compared to placebo. The middle panel depicts MCP-1, a pro-inflammatory cytokine that exhibits early and sustained reduction in CSF levels in the NurOwn treatment group compared to placebo. The right panel shows levels of Galectin-1, a neuroprotective biomarker that is increased immediately after NurOwn treatment and remains elevated at week 20. Importantly, all four biomarkers, including NfL, show a significant treatment effect overall, or a treatment by time effect across all visits. To me, the biologic impact of NurOwn across multiple biological pathways relevant to the pathophysiology of ALS in multiple biomarkers in these pathways in a direction of benefit to patients is most striking.

Using the same methodology that Dr. Wei introduced earlier, let's view the totality of evidence across these important biomarkers. As just reviewed, the NurOwn treatment group is better than placebo over time for each of these biomarkers. Using the totality of evidence, we

observe that the likelihood of observing this consistency in data if there were no treatment effect by NurOwn is very small. In fact, the p-value associated with that statistical test is less than 0.0001. This analysis provides strong statistical support of NurOwn's effect on biomarkers and over time.

NurOwn demonstrates evidence of a biological effect in data from all trial participants. This data reinforces the clinical outcomes from a trial. To summarize, there are three conclusions from the biomarker data review. NurOwn induces significant improvements on CSF biomarkers across pathways of neuroinflammation, neurodegeneration, and neuroprotection in all participants in the trial. The impact on multiple biological pathways and CSF biomarkers has not been seen in other ALS clinical trials. NurOwn significantly reduces NfL levels from baseline compared to placebo in the trial with P less than 0.05. The totality of evidence provides strong statistical evidence of a NurOwn treatment effect across biomarkers and pathways over time. Thank you. And I'll turn the presentation over to Dr. Taylor.

Safety — Dr. Kirk Taylor

Dr. Taylor: Thank you, Dr. Bowser. Good morning. I'm Dr. Kirk Taylor, Executive Vice President, and Chief Medical Officer at Brainstorm. I will now review the safety data demonstrating that NurOwn treatment was well tolerated with a manageable safety profile. I will cover both the data in all patients and those in the subgroup of participants with ALSFRS greater than or equal to 35.

Overall, a total of 157 adult patients living with ALS have been treated with NurOwn in the clinical program. An additional 17 participants are receiving NurOwn through the Compassionate Use programs, and there are an additional ten people in the Expanded Access Program. Today, I'll focus this presentation on the 95 participants from the Pivotal Phase III study.

Adverse events were balanced between groups and occurred in nearly all participants. In the overall population, more participants in the NurOwn treated group experienced serious adverse events. Although only two participants with serious treatment emerged in adverse events, were considered to have probable, possible, or definite relationship to the study drug, one participant in each treatment group. Few participants in either group had adverse events leading to treatment withdrawal or discontinuation. In the NurOwn arm, there were ten deaths versus four in the placebo arm. Two additional deaths occurred in the placebo group prior to treatment. The majority of the deaths, 75%, in the study were characterized as disease progression. None of the deaths in either treatment group were considered related to study drug.

In the pre-specified subgroup of participants with baseline ALSFRS of 35 or higher, more placebo treated participants experienced serious adverse events compared to those treated with NurOwn. Few participants in either group had adverse events, leading to treatment withdrawal or discontinuation. And lastly, there were no deaths in the NurOwn treated group and one in the placebo. Now let's turn to these categories in more detail across all trial participants.

Here are the adverse events with a frequency of ten percent or more in either arm. The most common AEs of mild to moderate severity were trans or procedure related AEs, such as the preferred term of procedural pain, headache, and back pain. These AEs occurred at higher rates with NurOwn than placebo. The majority of events were transient and manageable by physicians with typical standard-of-care and no lasting sequela.

Serious adverse events were consistent with ALS disease progression and occurred more frequently in the NurOwn group. Events occurring in five percent or fewer participants and dysphagia being the most common. Now turning to deaths.

There were a total of 16 deaths in this study, ten in the treatment group and four in placebo. Two additional participants in the placebo group died before receiving treatment, one due to disease progression and the other from cardiac arrest. No deaths were reported as related to study treatment by the investigator or the sponsor. 12 of the 16 participants, 75 percent, who died in the trial died due to disease progression. Eight participants on NurOwn and four on placebo. These participants started with comparatively low ALSFRS scores as shown in the highlighted column. These scores continued to decline as shown in their last visit measurement.

As an autologous stem cell therapy, NurOwn is not expected to have any drug-drug interaction potential. Thus, formal drug-drug interaction studies have not been conducted. Furthermore, as NurOwn cells are the participants own cells, there is no risk of rejection and no need for immunosuppressive agents, which can cause severe and or long-term side effects.

In summary, NurOwn treatment was well tolerated and had a manageable safety profile. Most events were transient and mild to moderate in severity. There were a few individual reports of serious adverse events. Most of the deaths were caused by disease progression, which is consistent with their advanced disease. In the pre-specified subgroup of early disease participants with ALSFRS of 35 or more, we observe a lower rate of SAEs and no deaths in the NurOwn arm. Overall, NurOwn has a manageable safety profile with a favorable benefit risk ratio. Thank you. I want to now turn the presentation back over to Dr. Windebank.

Benefit/Risk & Clinical Perspective — Dr. Anthony J. Windebank

Dr. Windebank: Thank you, Dr. Taylor. As someone who treats people with ALS and has been involved in biomedical research and clinical trials for more than 40 years, including as the Mayo Principal Investigator for the NurOwn Phase Two and Phase Three trials, I would now like to provide my clinical perspective on NurOwn.

The FDA has approved four treatments for ALS. None of these drugs are curative, but they all help patients manage and stabilize this horrible disease. It's promising to see that the FDA has exercised regulatory flexibility in bringing all of these products to patients. These approvals came after some of the trials have missed their primary endpoints, and in some cases, following post hoc analyses. Given the unmet need that remains, I hope that the FDA will continue to exercise the broadest flexibility in applying the statutory standards for this life-threatening disease.

I want to be clear that the FDA and investigators have the same goal. We all want safe and effective therapies for patients and we all work tirelessly towards that goal. I also want to be clear that safe and effective doesn't always mean a cure. In fact, in our world, it rarely does. As someone involved in ALS and cancer research for decades, we've seen incredible advances in cancer treatments built on many incremental studies. To me, ALS is where cancer therapeutics were 40 years ago. And we need to take the same approach and build on research and incremental research. The FDA has exercised regulatory flexibility in drug approvals and promises to continue to do so. We need to work together to harness incremental steps so that ALS therapy can evolve in the same way as cancer therapy. Importantly, we can't afford to lose a potentially valuable treatment simply because of complex data. Let me summarize why I find this data compelling and importantly, why I believe it should be approved.

While it's clear this trial did not meet its primary point, it did meet nominal significance in an important pre-specified group. To me, these results show a true clinical benefit for an important group of patients. And Dr. Wei showed us statistically using a broad measure of totality of the evidence that these results are highly unlikely to be due to be by chance.

Additionally, it's clear that this trial enrolled a substantial number of people with advanced disease whose data were uninformative because of the floor effect. And when we look at the largest subgroup that includes all patients who are not impacted by the floor and are thus formative, we see compelling and consistent differences between NurOwn and placebo. And this is further supported by the biological effect on CSF biomarkers across all patients. Although the change in individual biomarkers is relatively small, the totality of evidence analysis is also extremely compelling. These results demonstrate a biological effect where the bounded score was insensitive to clinical change and informs me that NurOwn is providing a benefit across the spectrum to people with ALS. Additionally, I believe NurOwn has an acceptable safety profile and I have no concerns about treating my patients with this product. Although there are small differences in deaths between NurOwn and placebo, in my opinion, the degree of deaths is not unexpected, especially when you consider that those unfortunate deaths occurred in those with advanced ALS. I also want to point out that while this procedure is not a pill, the procedure was well tolerated by participants. I know this. I know firsthand how devastating this disease is, and I can assure you that patients are not concerned about a spinal tap when they are facing a rapidly progressive terminal illness.

Let me take a very brief moment to address overall safety of MSCs. First, MSCs have been researched for more than 30 years with more than 200 studies of MSCs in CNS diseases in the U. S. alone. A meta-analysis summarized safety of MSC administration over the past 15 years showed that they're safe in different populations. This was a formal systematic review. MSCs were isolated from several tissues across 62 randomized clinical trials covering 3,546 patients. No serious safety events other than transient fever, administration site adverse events, sleeplessness, and constipation.

As a clinician investigator, I also look closely on the aggregate data. While it is clear that not everyone responds to the treatments, there are clearly a significant number who do, and the response is very meaningful. I have clearly seen that some people stabilize in a way that I've never seen in any other trials. In fact, in the small number of people who participated in the expanded access program and received six to nine treatments, there were people who stabilized while on treatment in the trial. In the interval before they were in the EAP, which was over a year or more in some cases, these participants deteriorate. They again stabilized in the additional treatment period. There were also some who improved their score from baseline. Something that is rarely seen, and I should stress other investigators who have been working hands on with the participants in the trial have seen similar response. Let me give you a few examples of some of these changes in daily activity. These include walking without a walker, using the bathroom or showering unassisted, speaking more clearly, and breathing more strongly. These are huge. I can tell you that the value of any form of independence or stabilization for these patients is beyond words. And for these reasons, as a physician who cares for patients, I want to see NurOwn made available for people living with ALS. Cancer therapy would not have moved forward in the way it has without taking advantage of incremental steps. We have the same opportunity here. The sponsor is working on a Phase Four trial, but patients can't wait. As one physician scientist neurologist posted in the FDA docket for this meeting, 30,000 individuals with ALS will die while waiting five years for the results of another trial. There are thousands beyond me who want to see NurOwn available for people with ALS, each of whom is a person with a family where every day of life is treasured. Thank you. And I will now return the podium to Dr. Lindborg to take your questions.

Q & A

Dr. Ahsan: Thank you. Actually, I think Dr. Lindbergh, you had requested 5 minutes potentially to respond to the previous presentations. Would you like to do that now, before we get to questions?

Dr. Lindborg: We'll continue to Q and A. Thank you.

Dr. Ahsan: Okay, great. All right. So, if members of the committee can raise their hands and while others are getting to it, Dr. Alexander, can you go on camera and unmute yourself, please?

Dr. Alexander: Thank you for that informative presentation. I understand that there are four trials that are contributing to the evidence we're reviewing, but that only one of them is of the dose and route of formulation that's being proposed for market. Why did the Phase Two study use muscular injections if neurotrophic factors can't cross the blood brain barrier? And it's posited that that the treatment promotes neurogenesis and neuronal survival and function when, and I'm quoting from the briefing document, used in close proximity to damage motor neurons in the central nervous system.

Dr. Lindborg: I'll have Dr. Windebank respond to this question, but I do want to make 1 clarifying point from an earlier statement about the Phase Two trial. The objective of that trial was safety of intrathecal administration, and this was met so it was not powered and not a failed trial but I'd like Dr. Windebank to respond to this.

Dr. Windebank: Yes, so, the rationale for giving intramuscular injections close to the motor nerve endings was that we know that the motor nerve terminals in the muscle will take up factors close to them and retrogradely transport them back to the NurOwn cell body. So, it was a sort of secondary way to deliver neurotrophic or other potentially protective factors distally, specifically into the motor neuron, there was no evidence from that trial that it helped and it was the most uncomfortable for patients having 27 injections or so. And so, it was not included subsequently.

Dr. Ahsan: Thank you. Moving on. I think we have a question from Dr. Fischbeck. Can you please turn on your camera and unmute yourself?

Dr. Fischbeck: Thanks. This is very cogent and well-presented findings. I think I have a number of questions, but I tried to just get in one here about how were these cells made or selected to produce the neurotrophic factors, and what kind of quality control did you go through to establish that they continued to produce neurotrophic factors, in vitro or in vivo, how could you do that or how did you?

Dr. Lindborg: Thank you and I'll have Dr. Levy come respond to both of these questions.

Dr. Levy: Thank you, Dr. Lindberg. I am Yossef Levy, VP of Cell Production at Brainstorm. I have been working on Brainstorm for 18 years since 2005 at the inception of the company. I want to cite CM-10 please, to present to the panelists. So, during the production process we have in process control and final product or final product control characterization. So, the control is cell count, viability, identity, and potency, and also safety battery. We are releasing the cells only if we met all the quality control according to the specification that we have. Thank you.

Dr. Fischbeck: Oh, you know, so there's more to the question than that. My primary question is, how do you make these cells without genetic manipulation to produce neurotrophic factors?

Dr. Lindborg: Dr. Levy?

Dr. Levy: Thank you. No manipulation in our manufacturing process. Can I see slide number one, please? So, during our manufacturing process, we have a phase of the differentiation of the cell. This is a very short production process of three days that we put several neurotrophic factors, a chemical, into the culture of the cells. We are not doing any gene manipulation. Thank you.

Dr. Lindborg: And Dr. Fischbeck, since you asked a question about quality, I do want to note that of the 500 products that were made and for 200 people, 100 percent met the release criteria and were high quality.

Dr. Fischbeck: Okay.

Dr. Ahsan: Great. I think just to follow up with Dr Fischbeck's question a little bit more detail in terms of what the release criteria were would have been helpful. But let's move on. Dr. Lynn Raymond. Can you go on camera and unmute yourself?

Dr. Raymond: Thanks. Thanks for that presentation, everyone. So, I do also have a number of questions. So, I'm just going to do them, which is I heard in Dr Snyder's presentation that he had done a number of studies and really only, I think, one or two that they tried intrathecal injection, and those were neural stem cells where they found that they could survive if they tracked along nerve roots. So, I wondered if you have any preclinical evidence that the mesenchymal stem cells are surviving for any period of time or actually getting into tissue in the brain in preclinical models.

Dr. Lindborg: We do have evidence from a preclinical mouse model, and I'll have Dr. Windebank provide a little detail on that.

Dr. Windebank: Yes, this was a preclinical mouse model where the MSCs were injected, intrathecally and were found to be surviving and engrafting up to one month, which was the longest time point after intrathecal injection. We had done similar studies in rabbits and found similar sorts of findings as well and actually did prolonged pathological studies demonstrating no effect of tumorigenesis on these rabbit studies. Is that helpful?

Dr. Raymond: That's helpful. So, were they surviving in the CSF? Is that where you were looking? Or were they in actual tissue in the brain or?

Dr. Windebank: No, they, what they appear to do is to engraft on the lining of the inside of the CSF space, so potentially on the nerve roots on the inside of the fecal lining, but not penetrating into the neural tissue.

Dr. Raymond: Thanks.

Dr. Ahsan: Great. Thank you. Dr Mark Tuszynski.

Dr. Tuszynski: Hi, thank you for that presentation. Also, I have a lot of questions, but I guess we should cycle through so one person doesn't dominate. Let me just follow through on that last question about growth factors that Dr. Windebank just answered. Is there any evidence that the growth factors actually reach the parenchyma, the gray matter of the spinal cord where the alpha motor neurons are that you are targeting?

Dr. Lindborg: Dr. Windebank?

Dr. Windebank: I think that's a really tough question, of course, because you're looking at secreted growth factors, and we know that the intrathecal spinal fluid perfuses throughout the central nervous system, so it is essentially the extracellular fluid of the cells that we're dealing with. Now, have any measurements been made on whether the specific factors secreted by the MSCs reach a target? That would be difficult to achieve has not been done.

Dr. Tuszynski: Well, it can be done by an ELISA. For example, you take out the spinal cord and do an ELISA. That's been done in several other studies. Was anything like that ever done here?

Dr. Windebank: No, not that I'm aware of. And remembering that isolating neural growth factors from tissue and measuring by ELISA is going to have a huge amount of variability if you're looking for relatively small increases or increases relative to the total in specific cell populations. I can think of other ways to do it, but it would be quite complicated.

Dr. Tuszynski: Okay, well, with other approaches, it has been done, but sure. And then are you postulating that the growth factors access the gray matter of the lumbar spinal cord by diffusing through the central canal?

Dr. Windebank: Well, they could diffuse through the central canal or through, as you know, CSF movement in the spinal compartment. If we stick with that, it's kind of pulsatile. And it's moving throughout the whole of the CSF space for reabsorption in the ventricles in the brain. And that CSF turnover, part of the initial calculations in the preclinical studies was to say, well, how much growth factors would you have to have secreted by cells into this total CSF volume to achieve a therapeutic effect at the extracellular level using things like receptor binding studies to understand what potential therapeutic effects were? So, it's not just through the central canal, it's through the whole CSF space.

Dr. Tuszynski: Okay. I asked the question because I thought a diagram from the submitted documents show that the access was through Central Canal in part. And along those lines, I was going to say that the central canal in humans is vestigial below the cervical level. So that wouldn't be a root in humans where it would be in mice.

Dr. Windebank: Completely agree.

Dr. Ahsan: Okay. We do have a good number of questions still pending if we can focus on our most urgent question, and then cycle through, and then if we need to, we can find some additional time to follow up with questions. So, Dr. Gil Wolfe, if you could go on camera and unmute yourself.

Dr. Wolfe: Yeah, thanks again for the presentation, the baseline characteristics, again, the randomization basically work the one-to-one randomization, but I noted that the patients with bulbar-predominant findings were actually less. On active therapy, whether it was the whole

population or the ALSFRS-R, greater than or equal to 35. In light of that, given what bulbar involvement does for ALS patients, which is not good, obviously, what are your thoughts on what impact that may have had? It was about a 10, 15 percent difference. And I don't know if that was looked at more closely. The second question, this is an extension of Dr. Alexander's, I'll be quick. The Phase Two study enrolled milder patients. The ALSFRS-R, I know that was not the primary outcome, and this was one intrathecal injection. But when I looked at the curves, they are exactly on top of each other. So, your thoughts on that as well.

Dr. Lindborg: Okay, I'll take them in that order. So, the imbalance and I'll put up this slide on limb and bulbar versus bulbar, so you can see that there were more individuals with limb and bulbar in the placebo group then then NurOwn as you're suggesting. And with all of these, we had five variables that we know impact prognosis as you're pointing out, these were identified and were carefully looked at in terms of where their differences in the baseline characteristics. Did they influence the outcomes the clinical outcomes? And so, for example, was there a treatment by site of onset of disease interaction, and none of these bared out as impacting the conclusions? Number two, in the Phase Two data, the inclusion criteria was five points higher than in the Phase Three trial. And if we could bring up the fast progressor ALS suppressor data, what we see in in this study, and this was only one treatment, but what we observe is less function being lost. This is actually showing the difference in the slope from pretreatment, and we can see the impact in these fast progressors. It was a pre-specified group. It's approximately half of the trial, and we see a difference that is pronounced with bigger changes, meaning more stabilization in NurOwn-treated patients rather than placebo, which were declining.

Dr. Ahsan: Okay, thank you. Moving on to Dr. Rajiv Ratan. Can you please turn on your camera and unmute yourself?

Dr. Ratan: Yeah, thank you for the presentations. My question, I had a number of questions, but I'll ask one. It seemed in the domain analysis and the biomarker analysis that there was separation at the first time point measured, but we weren't shown earlier time points, which were demonstrated that actually the populations weren't different at baseline. Could you clarify that?

Dr. Lindborg: I just want to make sure I understand your question. So, the baseline characteristics…

Dr. Ratan: Right. So, when you show the different domain analysis, subdomains of the ALSFRS-R, it seemed like in many of the domains, the change was apparent already at two weeks. And we were never shown earlier time points showing that at baseline before treatment there actually were differences. In some of the domains there were differences, but you saw that at eight weeks and you might expect that there would be a delay if indeed that the stem cells were having an effect.

Dr. Lindborg: Yeah. Thank you. I understand the question. Thank you for clarifying. So, in our analyses if we put up for example, I'm happy to show the biomarker data, we actually displayed it in the core presentation, looking at baseline values. So, you could see that in the majority of biomarkers, the baseline values actually were on top of each other. So, they were very similar. Neurofilament light was one, as you can see on the top left graph, placebo patients by chance started with slightly higher values than NurOwn, as you can see by the difference. We were always looking at changes, though. So, our analyses took into account at an individual level change from baseline and then looking at treatment estimates. So, if there were differences, they were accounting for these differences by individuals. And Dr. Bowser would like to make a comment.

Dr. Bowser: Hi Raj, Bob Bowser. Good question. Yeah, with respect to the biomarkers, which in a few, yes, you see sort of a blip up in two weeks, and that's likely due to secretion of the marker in question, often a protective marker, in this case, I collected one by the cells themselves. And so, you're getting this quick increase two weeks after the initial dose that one can detect them very quickly in the CSF.

Dr. Lindborg: And in that case with Galectin, it was maintained through the end of the trial with an increase in Galectin and had a 13 percent increase from baseline. So, one of the important things and why we showed the biomarker data over time is that you can see quick changes in some biomarkers over others it's really the sustained effect and the biggest effect observed at the end of trial, which was true for [indiscernible]. Did that respond to your question?

Dr. Ratan: And what about the domain, the ALSFRS-R it didn't look like the same for those it looked like there wasn't a best baseline measurement but maybe I'm not remembering the slide well.

Dr. Lindborg: Yeah, the way that we displayed this data is in terms of changes from baseline and so both of the two weeks would start at zero and again going back to how we analyze the data. We didn't see major imbalances, but it would have inherently been brought into the calculation by looking at a change from baseline. So, if there were individuals that had higher or lower values, it's actually a very heterogeneous disease, then we would be accounting for that at a patient level.

Dr. Ratan: Great. Thank you.

Dr. Ahsan: Okay, great. I do want to thank the sponsor for their presentations. We do have a list of questions still, and we will find time later today who I have on in order would be Drs Liem, Wu, London, Gold, Nolta, Andrew Buckley, and then Caleb Alexander and Fischbeck. but

we will get to that later today because we have a hard end for lunch right now to prepare for the Open Public Hearing. So, we will reconvene at 1:40 and I think we'll be there until then. Thank you.

Open Public Hearing

Dr. Ahsan: Welcome back. We are about to start the Open Public Hearing portion of the afternoon. I have noted those who had questions. At this time, if they would like, the committee members who have their raised hands can lower them. I have an announcement that I will be reading, "The Open Public Hearing announcement for particular matters involving specific parties".

Welcome to the Open Public Hearing session. Please note that both the Food and Drug Administration (FDA) and the public, believe in a transparent process for information gathering and decision-making. To ensure such transparency at the Open Public Hearing session of the advisory committee meeting, the FDA believes that it is important to understand the context of an individual's presentation. For this reason, the FDA encourages you, the Open Public Hearing speaker, at the beginning of your written or oral statement, to advise the Committee of any financial relationship that you may have with the sponsor, its product, and if known, its direct competitors. For example, this financial information may include the sponsor's payment of expenses in connection with your participation in this meeting. Likewise, the 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. I will hand it over to Marie DeGregorio to read the rest of the Open Public Hearing statements.

Mrs. DeGregorio: Thank you, Dr. Ahsan. Before I begin calling the registered speakers, I would like to add the following guidance: the FDA encourages participation from all public stakeholders in its decision-making processes. Every advisory committee meeting includes an Open Public Hearing (OPH) session, during which interested persons may present relevant information or views. Participants during the OPH session are not FDA employees or members of this advisory committee. The FDA recognizes that the speakers may present a range of viewpoints. The statements made during this Open Public Hearing session reflect the viewpoints of the individual speakers or their organizations and are not meant to indicate agency agreement with the statements made. In fairness to all OPH speakers here today, since this is a 1-hour session, we ask that you please remain within your 3-minute time frame. To assist speakers and adhere to 3 minutes each, for each presentation, we are placing a timer in the lower left of the screen. We greatly appreciate your cooperation with this. When I call your name, please unmute your microphone and camera, if you would like to show yourself on camera, that is, and start your presentation. If you're not available at the time we call upon you, we will come back to you after the other speakers have spoken. We will now begin with Mandy Bailey.

Mrs. Bailey: My name is Mandy Bailey and I have no disclosures. I lost my stepdad to ALS in 2018 and I'm here today to ask for your vote in favor of recommending approval of NurOwn. When my stepfather was diagnosed with ALS, we were given no options. He was sent home to get his affairs in order. We watched helplessly as my stepdad went from a fiercely independent man who lived life his fullest, to a person trapped in a broken body who was left to watch the world pass him by. We learned very quickly to recognize the importance and value of every minute we had with them. One point on the ALSFRS-R scale would have meant more meaningful moments and memories with the person we loved. One point could have meant that my mother got to spend

more time with my stepdad as his wife and not as his nurse and caregiver. One more point could have meant that my children had the chance to learn more about the world from their Papa's shoulders before his speech became too slurred to understand and his arms were too weak to hold them. One more point could have meant that he would have been able to meet his oldest son's first child before he took his final breath. One more point could have given him the motivation to keep fighting instead of leaving him wishing for death. Every point matters.

My stepfather was also a proud U.S. veteran. Today, I represent not only him but also my friends and fellow advocates, the "I Am ALS Veterans" team. Each of the faces on this slide, represents a person or family impacted by ALS, as a result of service to our country. In his 2007 Congressional testimony regarding ALS, Brigadier General Thomas R. Mikolajcik said that if these soldiers were dying in the field rather than quietly at home as a consequence of their service, we would leave no stone unturned. We would use the best existing resources and programs to make sure they had whatever they needed to survive, to ensure that no man or woman was left behind. General Mikolajcik died from ALS in 2010. Our team is asking you to turn this stone over. Don't leave any more of our veterans on the field.

If you question the efficacy of NurOwn, please look at former Navy pilot Matt Bellina. Matt began to feel the positive impact of NurOwn almost immediately. Four months after he began treatment, Matt was able to stand up by himself without assistance, something he hadn't been able to do for over two years before NurOwn. He was even able to regain function that would allow him to control his power chair, by himself, and adjust his sunglasses. These bits of independence may seem small to some, but I can assure you, they are monumental and meaningful. In addition to regaining function, Matt's breathing improved so much that he was still feeling the effects, months after his treatments ended. Matt is living proof: NurOwn is safe and effective.

Today I'm asking you to vote to recommend approval of NurOwn. The community recognizes that this isn't a perfect cure and it isn't going to work for everyone. But with a disease like ALS that is 100% fatal, some is enough. One point is enough. One point could mean the difference between living to see a cure and dying waiting. Please vote to recommend approval of NurOwn. Thank you.

Mrs. DeGregorio: Thank you, Ms. Bailey, for your testimonial and for sharing that with us today. Next in line, we have Ms. Andrea Goodman.

Ms. Goodman: Thank you so much. My name is Andrea Goodman. I am the CEO of "I Am ALS" and I have no disclosures. I consider it an honor to be a part of this community-led organization. We don't just provide services or resources, we facilitate a public movement to end ALS. My career has been focused on the same frustrations that many of us share about the systems that were set up for us and often do not work for us. Achieving the health outcomes we want to see quickly, means choosing innovation over bureaucracy, not using scales and models just because they've always been used. It means noticing those whom the system does not serve and ensuring their needs are being met. People living with ALS are not getting their needs met. This disease is brutal. Let us be brutal and bold in our fight back. We know now as a field, that listening to people with lived experience and trusting they are experts, is imperative. Data comes from a variety of sources, including, and importantly, the knowledge that comes with lived experience. Never is that more important than with a fatal condition like ALS.

One community member said, "I knew there was something wrong with my body long before the medical science validated what my body was telling me. Believe the people who improved when receiving NurOwn. We know what it feels like to die a little more each day and we also know when therapy stops our symptoms or slows our paralysis." Unfortunately, many who

had the opportunity to use NurOwn through EAP or Compassionate Care programs are largely missing in the data being shared today. These are the very people living with ALS who know how it impacted their breathing, their movement, their increased function, or their reduction in decline. To fully evaluate this therapy, we must understand these experiences. This drug is not the cure we were all desperately hoping to find soon, but it does not need to be for its effects to be transformative for people living with ALS.

Today is a chance to make a real difference and help us take another important step toward making ALS a chronic, manageable disease. So, I ask you, one, to remember that testimonies are critical to contextualizing the data presented today. People living with ALS are the authority on what constitutes a meaningful effect and impact on their health and quality of life. Keep them foremost in mind as you make your decision. Two, consider the evidence with the same flexibility given to all previous ALS treatments. And remember that this is a disease with a serious unmet need. Lastly, please remember the value of the lives of the people with ALS and their desire to access NurOwn. Thank you for your time today.

Mrs. DeGregorio: Ms. Goodman, thank you so much for your story and for sharing your perspective with us. Next up, we have Mr. Phillip Green.

Mr. Green: I have no disclosures. My name is Phillip Green, a 53-year-old husband and father of four, who was diagnosed with ALS in August 2018. I participated in the Phase 3 NurOwn drug in 2019 and in January 2021, I was selected for the NurOwn EAP. After treatment in March, I was able to do certain things with my hands that I had lost the ability to do. I could once again, pick up my phone and the TV remote and use them without dropping them. I was now able to grab my pill box, open it, dump the pills onto the countertop, pick up each pill with my fingers, and place them in my mouth. These small gains wouldn't show up on the ALS FRSR, but they gave me back some

independence I had lost. In June, I began to gain strength in my legs. I was now able to stand in my pool, where before the EAP, I couldn't even walk out my legs. I could now do squats in my pool and even walk along the edge of my pool. I could again buckle and unbuckle my seatbelt on my own. These changes were meaningful to me, but would not be reflected in the ALS efforts. I received additional NurOwn treatments in 2022. After receiving treatment in March, my FEC went up 11 points, to 45% predicted. My speech was no longer impacted by shortness of breath. My breathing has remained strong, and my FEC earlier this month was 37% at the clinic. I'm here to tell you that NurOwn works. I know it worked for me. It has helped me maintain an active and productive quality of life. I strongly urge you to consider the totality of that and recommend approval, so the person diagnosed with ALS today or tomorrow can retain as much function and independence, for as long as possible. Thank you.

Mrs. DeGregorio: Mr. Green, thank you. We are deeply appreciative of your sharing your thoughts and personal story with us. We appreciate that. Thank you. Next, we have Mr. Robert Hebron.

Hebron: Thank you. I have no disclosures. I submit that this ADCOM Panel has both a critical and difficult question to answer regarding NurOwn. Namely are a large number of positive patient-reported outcomes to be believed, despite the clinical trial failing to meet its primary endpoint. We know that the NurOwn safety profile is well-proven. We know that patients have documented improvements and even reversal in disease progression, something virtually unheard of in ALS. I submit to you that the evidence coming out of the trial indicates that the patient-reported outcomes are to be believed and the treatment warrants approval.

To better understand, it's necessary to critically evaluate the trial's primary endpoint. A clinically significant slowing in disease progression is measured by the ALS FRSR scale. That

scale is a somewhat subjective quality-of-life assessment. Its ability to capture progression over a six-month trial can be questioned. Disease progression in ALS is not predictable based on a patient's prior progression pattern. Slope measurement is influenced by the so-called four-factor. Once a patient hits a zero score on some of the 12 rating factors, it becomes more difficult to discern further progression throughout the trial. If that patient lands in the control arm, it might misleadingly improve the control arm's mean result. In the treatment arm, it may result in a positive outcome not being captured in the data. Both types of results diminish the treatment's chances of showing efficacy. Moreover, randomization of these patients is unlikely to produce an even-handed allocation to the two trial arms.

Second, genetic sequencing of the trial participants post-trial by Dr. Brown, one of the investigators at the University of Massachusetts, found a large cohort, 60% plus of trial participants, had a mutation at UNC13A that predisposes individuals to ALS. My daughter is pictured here and has that mutation. Such individuals, tend to progress faster and differences in progression are more easily recognizable for them. The same genetic-based observation was also seen in an earlier European-based trial of lithium bicarbonate in ALS. Notably, when one excludes the first cohort where progression is difficult to discern, and when one only looks at the second cohort where progression is easier to discern, the trial meets its primary endpoint, in both instances. Those two different ways of looking at the trial population minus the confounding group suggest that finding of efficacy. For the reason that the problem with judging efficacy is not the data here, but the lens with which we view the data, ALS FRSR, a foggy lens, at best. For this precise reason, I urge the committee to look at the biomarker data because it becomes critical and definitive in assessing efficacy when evaluating the situation.

My daughter, Beth, was diagnosed with ALS almost 10 days before the date of this ADCOM meeting. You're seeing her pictured here. The picture was taken recently, this summer. Despite my love for her, my appeal to you is not emotional, but a request to kick the tires harder. I ask you to look at the evidence with the same sense of urgency that I have and work to reach a consensus in answering the question I posed. The lives of ALS patients are worth that level of effort on your part as committee members, as is the use of regulatory flexibility to resolve difficult questions when confronting such a terrible and to date, untreatable and always fatal disease, especially in light of the many positive patient-reported outcomes. Thank you.

Mrs. DeGregorio: Thank you, Mr. Hebron. We are very grateful for your comments. Thank you for sharing your thoughts and your story. Next, we have Ms. Mitze Klingenberg.

Ms. Klingenberg: Thank you. I have no disclosures. My name is Mitzi Klingenberg. I am a 40-year-old nurse and Matt Klingenberg's mom. ALS is killing my son. Today, you have the opportunity, the power, and the moral obligation to give him more quality of life with his family. I say this because NurOwn works on my son, Matt. Matt was diagnosed in March of 2018. He met the run-in phase criteria, and in January 2019, he began the Phase III NurOwn Trial at Mayo Clinic. Matt's fasciculations decreased immediately. He did not progress until late 2020. For 20 months, he had no changes in his overall physical abilities. He worked, wrestled with sons Mason and James, and ran his usual 3 miles. The trial is blinded. Matt's lived experience is not blinded. Without NurOwn, Matt progressed. Gross motor and fine motor skills declined, resulting in falls, less balance, difficulty walking, hands that didn't hold silverware, or the kids. Next slide. Here are videos of Matt during the 6-Dose Expanded Access Program in ‘21 and ‘22. We have many before and after videos. When he got NurOwn, he didn't progress and improved in areas. Matt had fewer falls, walked faster, had better balance, opened food packages, and snapped James, his son, into

his car seat. Next slide. This is a before-after of his arms. This kind of improvement, allows a person to touch their face, swoosh a fly, and scratch an itch. His voice improved. He had near-normal cadence and strength. He stated, “Mom, I feel whole! I feel like my body's working again!” Next slide. He walked with a stronger gait, heel-to-toe, on grass. Matt's walking improved so much that Mason, then six, commented, “Daddy, you're walking better!” A six-year-old saw this. A six-year-old saw his dad walking better. It's that obvious. Next slide. When Matt is on NurOwn, it helps him. When he's off of it, he gets worse. His progression was cyclic, as related to receiving NurOwn. Matt had 13 lumbar punctures and 2 bone marrow extractions. These were not a problem. In Matt's words, “It was well worth it!”

Today, Matt is 5 and a half years into his illness. He can eat, talk, breathe, and walk with a walker. This treatment helps him fight this disease. He gained function with NurOwn. We know with absolute certainty that NurOwn had a clinically meaningful benefit. To our family, this is substantial evidence. Matt, Kelly, and all of our family implore you to approve NurOwn. Thank you.

Mrs. DeGregorio: Ms. Klingenberg, thank you so much for speaking on behalf of your family and your son. We greatly appreciate your comments. The next person in the queue is Mr. Joe Morris.

Mr. Morris: I have no disclosures. My name is Joe Morris. I'm the husband and former caregiver of my wife, Sandy, who passed away from ALS in August of last year. Sandy and I spent 33 years of our lives together, raising three children in Lake Tahoe, California. Shortly after her diagnosis at age 51, Sandy did not waste any time, carefully researching the ALS landscape and becoming a powerful patient advocate to ignite change with her limited time. She spent her diagnosed life leading the original “I Am an ALS” teams, including legislative affairs, community outreach, and

clinical trials. She was a driving force and passing act for ALS and reformed the ALS clinical trial process. Sandy led a team that drafted and published a roadmap for people who are living with ALS and how they demanded to be treated by all stakeholders. The team that spirited this project alongside Sandy named these guidelines after her. They're known in the community as Morris ALS principles. Sandy was enrolled in the NurOwn Phase 3 Trial and was selected to receive expanded access in ‘21 and ‘22. We have heard a lot about the floor effect in the presentation from this morning, but I'm here to share with you my family's lived experience with NurOwn.

Before the first round of EAP in ’21, Sandy's diet primarily consisted of soup. Shortly after receiving her first dose of EAP, Sandy was successfully eating not only full pieces but entire rolls of sushi. In a disease that you do not expect to revisit function that had already been claimed by ALS, this improvement in her swallowing was an absolute home run for our family and boosted Sandy's quality of life. In addition to her improvement in swallowing, Sandy's air hunger notably decreased. Her voice became more easily understood. This allowed Sandy to continue to effectively communicate and remain powerful and purposeful within our family and continue driving her advocacy efforts to qualities of life that were non-negotiable. These improvements will not show up on your ALS FRS-R scale, but my family experienced the small, yet monumental, benefited function. We celebrated quarterly, every day of the last two years with Sandy after she received expanded access. It is important to note that Sandy received expanded access in the most advanced stage of ALS. She was not in the statistically significant group, yet, she still experienced meaningful treatment effects. The change that my wife fought for, the improvement that my family experienced firsthand, and the real potential of what this committee has in front of them today are truly life-changing. It certainly was for our family.

I urge the committee to vote to approve NurOwn. I'd like to finish with a quote from Sandy: "We must work quickly to save the next ALS vintage and possibly some of us from this one. Please hurry! The waiting is deadly!" Thank you for the opportunity to share my family's experience with this treatment.

Mrs. DeGregorio: Mr. Morris, thank you so much for your comments and for sharing your story with us. We do appreciate that. Next, we have Dr. Ajay Sampat.

Dr. Sampat: Thank you. I have no disclosures. My name is Ajay Sampat and I'm an Associate Clinical Professor of Neurology at the University of California Davis. I'm also a father of two young children, a husband, a son, a brother, and in the cruelest twist of irony, also a person who is living with ALS. I'd like to present three points about why NurOwn should be approved from my dual perspective as a board-certified academic neurologist and as a person who is living with this disease. Next slide, please. ALS is a clinically heterogeneous disease, which presents and progresses differently in each individual. As a result of this clinical heterogeneity, it will take an equally diverse therapeutic cocktail to make a tangible impact on progression rate and survival. As the only potential therapeutic in sporadic ALS that has an intrathecal method of delivery, NurOwn offers a particular promise that other approved treatments do not have: an advantageous method of delivery that bypasses the blood-brain barrier. The second key factor that separates NurOwn from the current FDA-approved treatments is its seminal biomarker effect across the disease spectrum, not seen in any of the currently approved therapies for sporadic ALS. NurOwn was found to reduce biomarkers associated with neurodegeneration and neuroinflammation and increase markers associated with neuroprotection.

Now, as a neurologist, I always feel more confident when there is objective data that correlate with clinical outcome. While these two facts are important, the most compelling

argument I can make for the approval of this drug is its role in preserving function, which is beyond clinically meaningful for every ALS individual and their families. Next slide, please.

The Phase 3 trial of NurOwn demonstrated, on average, a 2-point slowing of progression on the ALS FRS scale for 77% of trial participants over 28 weeks. While this may not seem like a lot, for someone living with ALS, two points are significant and clinically meaningful. For me in particular, those two points could mean the difference between reading my kids a bedtime story at night or not. It could mean the difference between using my BiPAP device only at night or having to use it during the day as well. It could mean the difference between me being able to still give lectures as a clinical educator or losing yet another vital part of my identity. Any preservation of function as someone living with ALS is clinically meaningful. Please don't discount the human experience in this horrific disease. And remember, there is no risk worse than a certain death from an 100% fatal condition.

As a neurologist, if I were counseling a patient in my clinic, my risk-benefit deliberations would focus on the favorable safety profile of this drug, the critical unmet need of ALS with no other viable treatment alternative, and the potential for even modest improvements in a patient's quality of life. As a neurologist, I would feel confident recommending this therapy to my patients and as an ALS patient, I would feel confident accepting this therapy from my neurologist. Please vote to approve NurOwn for all people living with ALS. Thank you.

Mrs. DeGregorio: Dr. Sampat, thank you for sharing your comments, thoughts, and your testimony on that. Thank you. Next, we have Ms. Candy Simons.

Ms. Simons: I have no disclosures. December 10th, 2018 is the date on which the three letters ALS went from meaning absolutely nothing to our family to dictating the rest of our lives. My name is Candy Simons and I'm here representing my family. Most importantly, I'm speaking for

my older son, Cade, who was diagnosed with ALS at 21. I am here to ask you to recommend approval of NurOwn. With no family history, Cade was diagnosed just six months after completing his second year of collegiate baseball, a sport he loved and played since he was two years old. At 21, Cade was told that he would die within two to five years. Three months after his diagnosis, Cade started the NurOwn Phase 3 trial at Mayo with Dr. Windebank and staff.

While the trial is still blinded, I would like to describe our family's experience during the trial. First, Cade tolerated the bone marrow aspiration and 14 lumbar punctures without any issues. He would do it again tomorrow for a chance at NurOwn. Cade was a fast progressor, rapidly declining in function early in his diagnosis. Throughout the trial, Cade's decline slowed and then stabilized for about 23 months after his third and final trial injection. From the first trial injection, Cade told us how his body felt and functioned better. He moved more freely and was less stiff, with a greater range of motion. Cade's vesiculations drastically reduced and eventually stopped. His legs were stronger and provided more stability when standing. Casually crossing his foot over his leg was much easier. He grabbed utensils, bringing them to his mouth with more accuracy. Texting was easier. Cade's speech and enunciation improved. In this slide right here, two weeks after his first trial injection, Cade stated, “I feel good, but my left side feels too good!” He explained he was having to adjust to the new strength in his previously weakening legs. Each amazing task that I just mentioned, improved Cade's quality of life. They are clinically meaningful to Cade and anyone fighting this horrific disease. Today, Cade is 26 years old. He has no feeding tube and takes all nutrition by mouth. Cade still has strong legs and can help support himself while being transferred. He can uncross his legs in bed. Cade still communicates verbally and uses no breathing equipment. This amazing child of mine lies inverted in bed and can fall asleep in that position. That's how well his diaphragm muscles are doing, which is not typical of someone five

years post-diagnosis. I tell you this because COVID halted all collection of respiratory data during the trial. Knowing the trial is still blinded, our family strongly believes that Cade is doing as well as he is today because he was in the NurOwn trial. Four years ago, he gave his body to advance ALS science. It would be inhumane to deny Kate access to this drug because the FDA approval process didn't act as quickly as ALS is killing him. Please use your regulatory flexibility for this critical unmet need. No mother should have to watch their child die when we believe a treatment is available to help him live a life worth living. Thank you.

Mrs. DeGregorio: Ms. Simons, thank you so much for your comments and for providing your perspective on this. We very much appreciate it. Next is Mrs. Paula Smith and Josh.

Mr. Smith: We have no disclosures. Thank you for allowing me to speak today for the approval of NurOwn. It has given me the ability to do so as long as the chance in a longer, fuller life. My name is Joshua Smith. I am living proof of the success of this therapy. My ALS journey began 1,657 days ago, at the age of 29. Next slide. Before ALS, I played football for 13 years, earned a degree in criminal justice, and coached Middle School Football. I was an avid motorcycle rider and worked in the construction business with my dad. My strongest advocate, my mom, will continue to tell her story.

Mrs. Smith: Josh was fortunate enough to participate in the NurOwn clinical trial and continue with NurOwn through the Expanded Access Program. During this phase, I witnessed firsthand the positive impact that this treatment had on his life. The progression of his ALS slowed down, his arms and legs had regained strength, he could still raise his hands above his head, his vesiculations had slowed down, his speech had become clearer, and the quality of his breathing had improved by 40%. NurOwn gave him a new lease on life, allowing him to continue to do the things that he loved best. Next slide. Climbing into his Jeep and driving, going down 100 steps to a waterfall

while on vacation, eating anything he chooses, still playing fetch with his dog, and spending precious time with his loved ones.

Now, five years later, Josh still has his voice and is still using it to advocate for the approval of NurOwn, as it improves how he feels and functions. When he receives NurOwn, it halts his progression, and in some ways restores his functions. When not receiving NurOwn, he declines. It has been 13 months since the last NurOwn Injection, and he is losing his strength in his arms and his legs. Josh can no longer walk independently but relies on a walker or a scooter. He no longer drives. He can only go down one step in or out of our home. Vacations are getting harder as he continues to lose his function, and he now needs assistance with washing his hair and dressing. His arms no longer go above his head. Josh lives each day with a positive attitude. He taught this to his football kids. Perseverance goes a long way. Always have determination and never give up. We believe that NurOwn works. My son deserves this promising treatment. I will continue fighting this fight for him to receive it. My son is enough. He wants to live. Today we ask the committee to approve NurOwn. Josh is living proof that this treatment works. Together we can provide hope and a chance for a better future for everyone living with ALS. Thank you.

Mrs. DeGregorio: Ms. Smith and Josh, thank you so much for your testimonial, and we very much appreciate hearing the thoughts that you've decided to share with us today. Thank you. Next, we have Ms. Amanda Stevens.

Mrs. Stevens: I have no disclosures. My name is Amanda Stevens, and this is my husband, Eric. At just 29 years old, he was diagnosed with ALS on August 27, 2019, just one month after our wedding day. The first slide, please. His symptoms, slurred speech, and left-hand weakness began around March 2019. Before ALS, Eric played college football at UC Berkeley and then in the NFL with the St. Louis Rams. He left that career to become a firefighter, where he served the city of

Los Angeles for five years. With our two-year-old daughter Peyton, we will celebrate Eric's 34th birthday this Sunday.

Eric participated in the NurOwn Phase 3 trial from February to September 2020, and then the Expanded Access Program. From symptom onset through the trial's lead-in period, Eric progressed rapidly, losing about 2 points per month on the ALS FRSR. His left hand was getting weaker, his fasciculations were spreading, his speech was slurring, and he was choking on thin liquids like water. When he received NurOwn, every two months in the EAP programs, his progression of ALS stopped. Eric's fasciculations decreased and he had less cramping. His speech remained loud and clear, and he was eating a normal diet. His breathing remained strong. He was able to use the dexterity of both hands to tie a bow, peel open Reese's peanut butter cup, go fishing with his brothers, turn pages in a book, text, bathe, shave, and eat with a fork and spoon. Next slide. But most importantly, he was able to be a present father. He could read our daughter books, sing her songs, help bathe her, hold her, and walk her in her stroller. We know that he would not have been able to do any of these things had he not received NurOwn.

Eric's last EAP injection of NurOwn was in September 2022, exactly one year ago. Without NurOwn, he has declined. He notices the most decline in his hands and limbs. He can no longer feed himself with a fork or spoon. He can no longer bathe or dress himself. He can, however, still lift a mug to his mouth to enjoy his morning coffee and use his fingers to text on his cell phone. Four years later, Eric still speaks loud and clear and can still walk with assistance. Next slide.

In conclusion, we want to reiterate to this advisory committee and FDA officials that NurOwn works. It improves not just how Eric feels and functions, but also enhances his quality of life. He needs to continue to receive this drug so he can live a better life and be a present dad to our daughter, Peyton. Eric would like me to leave you with his words: “As a firefighter, I took an

oath to protect and serve. I laid my life on the line every day for others. I ran into burning buildings putting others' lives before mine. As doctors, you take a similar oath, to not harm. I am asking you to remember that oath, and listen to my testimony and that of our neurologists. Then act with the same urgency as I did when I ran into a burning structure. I am not asking you to risk your life for me like I did for others. I'm simply asking you to not stand in the way of getting more of the drug that is helping me live." Thank you.

Mrs. DeGregorio: Miss Stevens, thank you so much for sharing your personal story with us. We do appreciate that. Dr. Michael Abrams, you're next.

Dr. Abrams: Yes. Good afternoon. I'm Michael Abrams from the Public Citizen Health Research Group. I have no financial conflicts of interest in this matter. The analysis conducted by FDA scientists shows that debamestrocel cell autologously transplanted mesenchymal cells engineered to secrete increased levels of neurotrophic factor, or MSC-NTF for short, has yet to demonstrate effectiveness as a treatment for ALS. The single Phase 3 trial for this biologic drug failed to meet any of its pre-specified primary or secondary endpoints. Moreover, bioassay studies failed to show drug-induced cerebral spinal fluid concentrations that logically connect treatment with MSC-NTF to lab values or neuronal biomarkers and motor function in patients. Additionally, the FDA has not been able to verify that MSC-NTF can be reliably manufactured. In the 28-week Phase 3 study, 189 patients were randomized to MSC-NTF or the placebo. The study did not show a significant difference between groups in the proportion of responders to the biological drug, which is the primary efficacy endpoint. Six secondary endpoints were similarly negative for efficacy. There were 10 deaths in the MSC-NTF group and just three in the placebo group. Using Kaplan Meier analyses, this difference between groups was significant. After the fact, analyses by the sponsor found that a subsample of the highest functioning participants of baseline were significantly more

responsive to the MSC-NTF than to placebo. Such a post-hoc finding, however, was biased towards a false positive result and was invalidated by the FDA review showing that there was no evidence of a sponsored hypothesized floor effect regarding motor function declines from baseline through week 28. Laboratory assays and facility inspections have yet to verify the quantity and central nervous system dispersion of cells and trophic factors delivered with each injection. Although CSF sampling up to 20 weeks after the first MSC-NTF treatment did identify some biomarkers suggesting that biological drug protects neurons. These analyses were plagued by missing data in approximately half the sample, and the levels of the biomarkers were mostly not correlated with the functional outcomes. We thus agree with the FDA that this BLA for MSC-NTF should not be approved, and we encourage this advisory committee and the agency to reject the application. Although we recognize the urgent need for effective treatment for ALS, this application fails to provide reasonable evidence of the drug's effectiveness and safety. Thank you very much.

Mrs. DeGregorio: Thank you, Dr. Abrams, for sharing your thoughts with this committee and with the agency today. Next, we have Dr. Jeffrey Cohen.

Dr. Cohen: Good afternoon. I'm a neurologist specializing in multiple sclerosis for 40 years. I serve as Director of Experimental Therapeutics at the Cleveland Clinic Mellen MS Center. I was the principal investigator of the BCT 101 trial conducted by BrainStorm and was the first author of the resulting publication. Funding for the trial was paid to my institution. I have served as a paid consultant for many companies developing therapies for multiple sclerosis, but not for BrainStorm. MS and ALS are distinct disorders but have some commonalities. As we currently understand the pathogenesis of MS, multifocal acute inflammatory demyelinating lesions account for clinical relapses in MRI Activity. It is this aspect of MS pathogenesis for which the 20-plus approved

medications are primarily efficacious. In contrast, progression, the predominant cause of disability accumulation, is driven by diffuse compartmentalized inflammation and neurodegeneration, similar in some ways to ALS. The available disease-modifying medications demonstrate minimal efficacy against these mechanisms in MS. As a result, treatment strategies that slow or stop progression or promote repair are major unmet needs in MS therapeutics. Based on the results of the BCT 101 trial, transplantation of NurOwn shows promise to address these unmet needs. BCT 101 was a multi-center Phase 2 clinical trial conducted from 2019 to 2021 at four academic centers in the U.S. Eighteen participants with non-relapsing progressive MS received every other month three intrathecal injections of 100 to 125 million cells. The treatment was tolerated well overall with no deaths, clinical or MRI evidence of disease activation, or clinically significant laboratory abnormalities. Due to the open-label uncontrolled design, efficacy results need to be interpreted with caution. Nevertheless, at week 28, nearly 1/5 of the participants demonstrated clinically meaningful improvements in two quantitative NurOwn performance tests, the timed 25-foot walk, and the Nine-Hole Peg test, which is a substantially higher proportion than in two matched historical control groups. In addition, CSF mechanistic studies showed increases in multiple neurotrophic factors and decreases in multiple relevant immunomodulatory inflammatory biomarkers. There is a great deal of interest in mesenchymal stem cell transplantation among people with MS and the clinicians who care for them. Based on the encouraging results of the BCT 101 trial, my center would enthusiastically agree to participate in future studies of NurOwn in Multiple Sclerosis. Thank you for your attention.

Mrs. DeGregorio: Thank you, Dr. Cohen, for your comments and for sharing your thoughts with us today. Next, we have Ms. Eby.

Ms. Eby: Hello. Thank you. No disclosures. My name is Brooke Eby. I'm 34 years old. You may know me from a viral video of me using a walker at my friend's wedding, giving my friend a walker ride on the dance floor, and letting the bride limbo under my walker. But let me paint a broader picture of my life. I'm the youngest of three kids, so naturally I was the favorite until the grandkids came along and took my spotlight. But losing that role introduced a new one. I'm now the favorite aunt of three nieces and one nephew. I work in technology. I have a very cute boyfriend and an even cuter dog. And last year at the age of 33, I was diagnosed with ALS. Being diagnosed four years after symptom onset means on the day of my diagnosis, I was told that I was not allowed to participate in trials and that I could expect to live two to five years. At the age of 33, I could be your daughter, your sister, your friend, even a mother. Yet, two to five years to live. I was left hopeless, just like every other who's been diagnosed since the first one over 150 years ago. This community has become far too comfortable being hopeless. When any of you on this committee pictures your future, you get to dream about family, career growth, travel, and retirement. I see blankness. My future doesn't exist. I'm living a hopeless journey to an end we all know is coming with a disease like ALS. But rather than make hopelessness the heart of my story, I want to make my message about excitement, something the ALS community hasn't ever been given the opportunity to feel. I went from using a cane to a walker to a wheelchair in a matter of six months. I have no reason to believe that my progression won't continue unless I get a chance to try NurOwn. I've reviewed the NurOwn data and I've heard the trial stories, how it helped some people stop progression, and how people like me who couldn't walk started having more function.

So, let's talk about what I'm excited about. I'm excited that NurOwn could keep me in my current state of progression or even give my legs back some function. I'm excited I could give more walker rides to my friends at future weddings. I'm excited I could teach my nieces and

nephews how to throw a baseball and even hold out hope that I'd make it to their graduations. I'm excited I could tell my siblings we can plan another family trip instead of planning my advance directives. I'm excited to tell my boyfriend that we can make a plan without the fear that the end is coming, and maybe he won't have to piggyback me up every staircase we encounter. I'm excited to tell my parents to stop worrying that the debilitating stress they've had since my diagnosis could be lightened. But mostly I'm excited to tell everyone in my life that I love, that there is something to be excited about. With NurOwn, the risk is minimal. With ALS, the risk is inevitable. Please picture my face as it's the one that you have the power to choose from and please recommend the FDA-approved NurOwn. Thank you.

Mrs. DeGregorio: Ms. Eby, thank you so much for sharing your testimonial with us. We greatly appreciate hearing from you today. Next, we have Dr. Hoffman.

Mr. Hoffman: Yes. Hi, I have no disclosures and I'm not a physician. My name is Ron Hoffman. I am the Founder and Executive Director of Compassionate Care ALS, a nonprofit organization dedicated to caring for those living with ALS. I have personally worked with thousands of individuals and families living with this fatal illness, and I have witnessed hundreds of people participate in various drug trials in the hopes of improving their symptoms and extending their lives. I'm speaking not as a doctor or clinician, but as an observer with 26 years of experience in the field of ALS. During that time, I've been in the presence of incredible suffering among our clients, more than any of you could possibly imagine. This suffering takes place on many levels. Of course, there's the physical suffering of the disease itself, but there's also the emotional and spiritual suffering that can be even worse. This often has to do with a sense of being abandoned profoundly by life itself. All avenues of hope become locked to the point of feeling stuck and complete despair. A big part of our work at Compassionate Care ALS is to facilitate an interest

among our clients, potentialities, and possibilities. NurOwn stands out as an avenue of encouragement. And for that reason. I stand behind its approval. I took care of numerous people in the NurOwn Phase 2 and Phase 3 trials and a couple of people who received NurOwn through the Expanded Access program. This therapy encourages the possibility of sustaining independence for longer periods. Though the results might appear at times to be small, any extension of physical abilities can be incredibly important for those living with ALS, their caregivers, and their families. The ALS journey for our clients is a continual slide into physical incapacity. I can't tell you how many times I've heard those living with ALS lament the loss of some basic ability taken for granted by most of us. The simple act of drinking a cup of water or feeding themselves becomes a marker of independence and self-esteem. The ability to simply turn over in bed at night on your own, rather than having to ask for help, means a great deal to the individual with ALS and the caregiver who can rest more deeply. I have witnessed people in the NurOwn trial make real gains, such as moving from a liquid diet only back to one of the solids or from being unable to assist with transfers to being actively and helpfully engaged in the process. These examples and many others leave me wanting to strongly recommend approval for NurOwn therapy for distribution. With a terminal illness, such as ALS, small victories and ways to, maintain independence are profoundly important. My staff and I are dedicated to supporting any small or large successes our clients can achieve. NurOwn provides a new avenue to positive outcomes we are dedicated to supporting. If you could see what I see. Thank you for your time.

Mrs. DeGregorio: Mr. Hoffman, thank you for providing your view and sharing those comments with us today. Professor Dimitrios Karussis.

Dr. Karussis: Hello. Thank you all for allowing me to talk. I am the head of the Neuroimmunology Unit at Hadassah University Hospital in Jerusalem. I do not have any specific

disclosures to this presentation. I do not have any financial relations with BrainStorm after our very old Phase 1/2 clinical trial back in 2012. My motivation to talk in this meeting today is that we have so much experience. I think one of the best experiences was with the use of different types of missing human-type stem cells in ALS starting in 2006, the regular-type of missing human stem cells. Also, I was involved in the Phase 1/2 trial with BrainStorm in which 14 patients with ALS were treated intrathecally with the NurOwn cells, six patients were treated intramuscularly only in one hand, and six intrathecally in the first Phase 1 trial. So, in total, we had 26 patients from them. I would like very much to share with you the long-term safety observations that we have with these patients and also about their survival rates. First of all, it is interesting that now up to 15 years after the trial, we have not seen unusual side effects so, this is a very good signal for long-term safety. But what was extremely low, which I see as highly unlikely, is that the percentage of patients still alive after 15 to 16 years from the onset of the disease is close to 50%. Nine out of 12 patients treated intrathecally are still alive and partially functioning. To my knowledge, this is very unlikely as compared to any other cohort of ALS patients. This is also further confirmed by an additional 12 patients who were treated 10 years ago with regular mesenchymal stem cells and still, we see very high survival rates of nine out of 12 being alive more than 10 years. I believe that this safety and mortality data are very important because real-life observations, especially in the long term, can provide sometimes clues to see whether, especially on a rare disease, often diseases like ALS, we can use a different type of treatment. Otherwise, I would say that there are other examples, similar to medications in myasthenia gravis, eculizumab, which was negative in the primary endpoint and is used in specific subgroups of myasthenic patients. Also, there are a lot of medications used in secondary progressive MS, even though these initial studies have been negative. So, my view is that NurOwn cells can provide, both in terms of safety and mortality rates

and efficacy, much more than the existing therapies for ALS and should be approved as an alternative option for this orphan disease. Thank you very much.

Mrs. DeGregorio: Thank you very much, Professor Karussis, for sharing your thoughts and expertise with us today. Next, we have Mr. Wallach.

Mr. Wallach: My name is Brian Wallach. I am joined today by my wife, Sandra, whose voice you are hearing as ALS has robbed me of mine. We are testifying for ourselves. We have no disclosures. I want to thank CBER for allowing us to testify on video and to thank the members of the ADCOM for their time on this critical issue for the ALS community. As a reminder, the only question before the ADCOM today is, "Has substantial evidence of effectiveness meeting the approval standard been demonstrated by the evidence presented?" As a second reminder, the "approval standard" for ALS treatments is specifically outlined by the 2019 guidance issued by the FDA, which is as follows: "When making regulatory decisions about drugs to treat ALS, the FDA will consider patient tolerance for risk and the serious and life-threatening nature of the condition in the context of statutory requirements of safety and efficacy." Notably, Dr. Billy Dunn recently stated at the start of the ADCOM for another ALS treatment, "For these serious diseases like ALS and so many other neurological conditions, the maximum degree of regulatory flexibility, the broadest flexibility in applying the statutory standards is operational."

Concerning NurOwn, we believe that approval is merited based on the science and the data that the company has shared with the public and with the FDA. With HIV and cancer, the first treatments that were approved did not work for everyone but instead helped a subset of people with those diseases live longer. Today, there are four approved treatments for ALS. That being said, ALS is still 100% fatal. So, it is critical that we have treatments to create a cocktail that combined, help us live longer to see a cure. Just as we did with HIV and cancer. We have seen people living

with ALS who are a part of the EAP and who have ALS FRS scores all over the map, see real benefit from NurOwn. For some of them, it has halted their progression, and for others, it has been able to help them regain some function. This is not something one sees in a disease like ALS. These results are further corroborated by the biomarker data that BrainStorm presented today. This data builds on what we saw with Tofersen and provides critical insight into how NurOwn works, as well as who it will work for. There is only one right answer here. We just hope you have the courage to recommend approval. Thank you.

Mrs. DeGregorio: Mr. and Mrs. Wallach, thank you so much for providing your thoughts and perspective on this issue. Thank you. Next, we have Dr. Zuckerman.

Dr. Zuckerman: Thank you. I'm Dr. Diana Zuckerman, President of the National Center for Health Research. I was trained in epidemiology and was previously on the Faculty at Yale, a Research Director at Harvard, and a Bioethics Fellow at the University of Pennsylvania. I'm also a founding board member of the Alliance for a Stronger FDA, which is a coalition of industry and nonprofit organizations focused on ensuring funding for this very important agency. Our Public Health Think Tank focuses on the safety and effectiveness of medical products, and we do not accept funding from companies that make those products. So, I have no conflicts of interest.

Thank you for serving on this important committee. I know it's challenging to balance the desire to help patients who have a devastating disease while focusing on your role to provide your expertise. Especially given the conflicting information presented today and the implications for the FDA's reputation as a gold standard. I'll focus on a few key results from the Phase 3 study, which is the only controlled study to evaluate the treatment using the intended route and dose interval. There was no benefit for the primary efficacy endpoint. In fact, the chance that treatment was better than placebo was about 50%. It's like flipping a coin. None of the key secondary efficacy

endpoints showed any benefit. With all due respect, it is not appropriate to combine non-significant results into a significant trend because the more comparisons you make, the more likely one of them would have been statistically significant. But in this case, none of them were. Perhaps most importantly, more patients taking the treatment died. At 28 weeks, 10 of the 95 on the treatment arm had died compared to three deaths of 94 in the placebo group. So, that's more than triple the number of deaths. The Chi-squared analysis is statistically significant. The patients who died during this treatment are not here today, and I want to represent those patients' results, which haven't gotten much attention so far. The improvement at week 28 was the same for the treatment group as the placebo group: 14% improved. This should remind us that some ALS patients will improve even with no treatment. And that's why a controlled trial is so important and why individual success stories, however heartening, can be misleading.

In conclusion, patients deserve clear evidence so that they can make informed decisions. And we all deserve an FDA that approves treatments based on scientific evidence. Patients should have the option of being in a free clinical trial or expanded access, but it would be unconscionable for patients to pay for this unproven treatment, which they would do if the FDA approved it. Thank you so much for the opportunity to speak today. I appreciate it.

Mrs. DeGregorio: Dr. Zuckerman, thank you very much for offering your perspective to us today. This concludes the OPH portion of today's proceedings. I would like to say that we are grateful to each of you for sharing your thoughtful remarks today with this committee and with the agency and for taking the time to be with us today. We invite each of you in the OPH to watch the rest of the day's proceedings on the YouTube link I provided you with earlier. Thank you so much. We will now proceed with the next portion of our meeting, Dr. Ahsan.

Dr. Ahsan: Great, thank you. I also want to thank all the speakers during the OPH session. Hearing those various perspectives is a very important part of the day. We're now scheduled for a short break. We went a little bit over so, we're going to shorten this break to just six minutes. We'll return at 2:50 to move on to the next portion with the FDA presentations.

FDA Presentation: BLA125782, Application for Debamestrocel

Dr. Ahsan: Right. Welcome back, everyone. We're on a tight schedule, so we'll continue to move forward. We are now at the stage where we will see a series of FDA presentations, again, in the interest of time, if each speaker can introduce the subsequent speaker. So, I will introduce the first speaker, which is Dr. Tom Finn, who is the BLA chair and CMC reviewer in the Office of Cellular Therapy and Human Tissue, CMC Division of Cell Therapy.

Dr. Finn: Good afternoon. My name is Tom Finn. I'm a product reviewer in the Office of Therapeutic Products, CBER, and I will start off FDA's presentations for BLA 125782 for the use of MSC-NTF, also known as debamestrocel and NurOwn, for the treatment of ALS. We would like to thank the AC committee for the review of the briefing document in advance of today's meeting and for participating in the panel discussion today, and to Dr. Snyder for his excellent overview this morning of cell therapies for neurological indications. We would especially like to thank the patients, families, caregivers, clinicians, and community members who are participating today for this important public discussion and whose input is very valuable. Finally, we would like to thank the representatives of Brainstorm Cell Therapeutics who have provided their perspective on the clinical studies performed. FDA recognizes the importance of developing novel products for the treatment of this devastating rare disease. We would like to note that on Friday, September 22nd, 2023, the applicant changed the clinical indication from treatment of ALS to the treatment of mild to moderate ALS. FDA presentations

will cover the original indication, as that was the focus of the BLA, but the same review findings and general principles apply to both indications.

FDA's presentations this afternoon will cover product, clinical, statistical, and biomarker review discipline findings. We will then provide a summary of our findings based on the totality of evidence for efficacy from the data submitted by the applicant.

We would like to start off by listing our key observations to convey our major concerns with the BLA. From the product perspective, we do not believe that adequate product quality has been established. And due to the substantial degree of missing information, determining the manufacturing process is in an adequate state of control is not possible. From the clinical and statistical perspective, the results from the Phase II and Phase III studies failed to show efficacy. And the multiple levels of subgroup analysis are considered exploratory at this stage. Survival data are limited and unfavorable. Our evaluation of the biomarker data does not indicate a clear association with clinical outcome and do not appear to support the mechanisms of action proposed by the applicant. The totality of data for MSC-NTF do not support regulatory approval for either the original indication of treatment of ALS or the more narrow clinical indication of mild to moderate ALS.

I will begin the FDA presentations with our evaluation of product manufacturing. Since the purpose of the afternoon panel discussion and the voting question will be on clinical evidence of efficacy, the product presentation will focus only on relevant manufacturing concerns for the clinical trials and the proposed commercial product. Though it is not clear what impact product variability and the limited manufacturing controls that were in place for the clinical studies might have on the interpretation of the clinical data, we believe it is important for the afternoon

discussion to present some manufacturing in biomarker data that relate to the proposed mechanism of action.

MSC-NTF is an autologous product derived from a single bone marrow collection. The bone marrow cells are expanded and cultured under conditions to increase neurotrophic factor production to produce what the applicant calls MSC-NTF cells. Three patient specific lots of 100 to 125 million cells are generated from a frozen intermediate time to provide treatment at eight-week intervals. The product is supplied as a four-mil suspension of MSC-NTF cells in a pre-filled five-mil syringe. In the briefing document, the applicant has described manufacturing as one bone marrow aspirate yielding enough autologous cells to produce two to three years of treatment doses, with the treatment being an intrathecal dose at two-month intervals. However, this product is being reviewed for manufacturing safety and efficacy as conducted for the Phase III study and as described in the BLA. Product quality, safety, and efficacy beyond a total of three treatment doses is unclear and is not supported. Product quality data supporting up to a total of 12 to 18 doses from a single bone marrow collection is not present in the BLA.

A key mechanism of action that formed the foundation of the BLA is the secretion of multiple neurotrophic factors by MSC-NTF cells. Neurotrophic factors are proteins expressed in the CNS and the tissues the neurons enervate that play a critical role in the survival, differentiation, maturation, and neural outgrowth of neurons. Since their discovery decades ago, there has been interest in using NTF, Neurotrophic factors for the treatment of a variety of neurodegenerative diseases. Unfortunately, most clinical studies using purified neurotrophic factors, including for ALS, have failed, or have had disappointing results. Limitations in the delivery of purified neurotrophic factors in vivo, rapid turnover, and in some cases, serious side

effects have hampered their usefulness. Cell and gene therapies are an alternative strategy to deliver neurotrophic factors in vivo.

In our review, including early product development, we noticed significant variation in neurotrophic factor secretion of each neurotrophic factor, and the amount varied widely across different MSC-NTF lots. While it is expected autologous cell therapies will have significant variation by product lot, all developers are expected to identify sources of variation in their process and to establish appropriate controls. Only a single neurotrophic factor was measured for potency in the Phase III study, and it does not appear one neurotrophic factor can adequately represent multiple neurotrophic factors. We also noted neurotrophic factor secretion varies from the same frozen intermediate, so it appears the process itself may contribute to product variability. Further, neurotrophic factor secretion measured for product release under optimized conditions may not be reflective of secretion levels and duration under conditions expected in vivo.

The product is administered by lumbar puncture into the epidural space. Although the delivering cells into the CSF overcomes issues with crossing the blood brain barrier, it is unclear how far secreted molecules travel within the CSF and how long MSC-NTF cells persist in vivo. This could be very important since ALS affects motor neurons throughout lumbar, thoracic, and cervical spinal cord and motor neurons in the cortex of the brain. We found no correlation between product release properties and the level of CSF neurotrophic factors measured as biomarkers, and we saw no correlation of product properties with ALSFRS-R clinical scores.

The applicant reported increased levels of VEGF, neurotrophic factor, in the CSF in patients treated with MSC-NTF product, with a peak at roughly two weeks post-transplant. We would like to comment on three observations we made regarding the CSF levels measured as

part of the biomarker panel. First, we noted that the overall concentrations of each factor differed little from each other, with BDNF and LIF being the lowest and HGF the highest. However, across all patients and sample time points, the difference observed between MSC-NTF treatment and placebo was small.

Second, the absolute levels of VEGF, BDNF, and LIF were very low and generally far below the levels typically used in research studies on neuronal cultures, including motor neuron cultures. For example, highly purified versions of VEGF commercially available as reagents are used in the nanogram per mil range. A nanogram is a thousand picograms. The level seen in most VEGF, BDNF, and LIF CSF samples, however, was in the low picogram per mil range, and therefore of questionable pharmacological significance. For example, BDNF is a classic motor neurotrophic factor, and a focus of their Phase I studies, but the median levels across all post administration timepoints was less than one picogram per mil. Although it is not known how much neurotrophic factor might be needed to elicit a clinical benefit, secreted molecules would have to contend with dilution by the 150-mil total CSF volume and the CSF turnover of four times per day.

Third, we were interested in the reported increase in VEGF CSF levels at two weeks and other timepoints, and we noted that most of the increase appeared to be associated with a fraction of all samples in patients that had values well above the median. More samples at two weeks had higher levels, but the prevalence varied by timepoint, and in most cases was associated with only one or two timepoints of the six treatment intervals. Because the product is intended to function in patients through elevation of neurotrophic factor levels in the CNS. We performed an analysis of the elevated VEGF levels with clinical outcome. We found no clear trend in the improvement of ALSFRS scores in that fraction of patients that had elevated levels at one or more time CSF

timepoints versus all MSC-NTF treated patients or placebo. This was true even when excluding the floor effect or evaluating the new 35 or greater baseline ALSFRS score subgroup.

I would now like to focus on some concerns noted with manufacturing issues that could potentially add variability to the clinical studies. The applicant is using data from multiple clinical studies. However, demonstration that the product is comparable across these studies, especially considering manufacturing differences between them, was not conducted. We noted several levels of product and process variation. The potential impact to the Phase III clinical studies is not clear. In addition, the applicant is proposing changes to product manufacturing for the commercial process, which raises concerns about the comparability of the commercial product versus the clinical product lots. In general, such situations can make it more difficult to have confidence the commercial product will continue to perform as it did in the clinical studies.

The applicant refers to a dual mechanism of action with immunomodulation by MSC-NTF cells within the CNS as an important biological activity of the product. However, no immunomodulatory properties were measured as in process or final product release testing to ensure product quality of MSC-NTF cells. The only manufacturing control strategy for all relevant biological activities is neurotrophic factor secretion. MCP-1, as mentioned before, is an inflammatory cytokine measured in the biomarker study. Measurement of NTF levels for release does not appear predictive of immunomodulatory properties because we found no correlation between CSF levels of VEGF and MCP-1 in the same patient at any timepoint. And NTF levels measured for release do not correlate with CSF MCP-1 levels.

To summarize the CMC findings, we determined that critical manufacturing controls are either not in place and/or incomplete, rendering substantive review of the overall manufacturing control strategy not possible. Manufacturing consistency Has not been demonstrated because

sufficient manufacturing data has not been provided, product variability has not been explained and process validation has not been performed. Further, comparability has not been demonstrated. We do not believe that adequate product quality has been established because from an NTF secretion standpoint, the controls in place appear inadequate based on what is known about the variability of the product. And it is unclear that the cells have the capacity to produce enough neurotrophic factors in the patient. Quality based on immunomodulatory properties appears inadequate because no assessment is performed as part of manufacturing.

I would now like to invite Dr. Gumei Liu to provide FDA's clinical overview.

Dr. Ahsan: Excuse me. Thank you. Tom. Maybe someone could show, I think slides two and three with the outline and the key messages before Gumei goes on. Or can they, do you want to talk about those? Slides two and three.

Dr. Liu: Sure. So, the author of the presentation today, like Tom, already has gone through these CMC concerns and I will be providing an overview of FDA's review of the clinical studies and our statistics reviewer, Dr. Mary Lin, will then present the detailed analysis of the efficacy results, including subgroup analyses. And our clinical pharmacology reviewer, Dr. Xiaofei Wang will discuss the biomarker data. And I will be back then to summarize FDA's totality of evidence considerations.

So, here are the key points for today's presentation. First, critical manufacturer controls are not in place or incomplete, rendering substantial review not possible. Second, our adequate product quality is not well established. And third two randomized, double-blind, placebo-controlled studies failed to show efficacy. And fourth, survival data are limited and available in subgroup analysis or exploratory. Last, but definitely not least, biomarker data do not indicate a clear association between any assessed biomarker and the clinical benefit. So, for either the

original or new clinical indication data that are MSC-NTF do not support approval. So, if we could advance to the clinical overview slide, which is slide 15, please.

Yeah, and I think I haven't introduced myself yet. So, my name is Gumei Liu. I'm the clinical reviewer in the Office of Clinical Evaluation, OTPCBER.

The clinical development program for MSC-NTF included four completed studies. The two early phase studies, MSC-NTF-001 and 002, were small, single arm studies, which took place in Israel. These studies investigated the safety, tolerability, and feasibility of MSC-NTF. They are not included in FDA's advocacy review. The Phase II and Phase III studies, BCT-001 and 002-US, were both multi-center, randomized, double blind, placebo-controlled studies conducted in the US. The Phase III study was the only study designed to evaluate the efficacy of MSC-NTF using the intended dose and the route of administration. That is three intrathecal injections each eight weeks apart. The Phase II study used a different dosing regimen, but still provides some insight into the efficacy of MSC-NTF. I'll be focusing on those two studies for today's discussion. Additional clinical experience with MSN-CTF in ALS patients included an intermediate-size expanded access protocol, which involved ten patients who completed the Phase III study at the time of BLA Submission. There was also a compassionate use program in Israel.

As mentioned, BCT-001-US, the Phase II study, was randomized, double blind, and placebo-controlled. 48 adult patients with ALS were randomized at a three-to-one ratio to receive a one time, combined, intrathecal, and intramuscular administration of MSC-NTF or placebo. Each patient was followed for approximately three months pre-treatment and six months post-treatment. Key eligibility criteria included disease onset between 12 and 24 months, ALS functional reaching skill revised, ALSFRS-R total score of at least 30, and the upright slow vital

capacity, as we see, of at least 65% of that predicted for normal. The graph on the right shows ALSFRS-R total score over time for the full analysis set, which included all 48 patients. 36 in the MSC-NTF group, showing blue, and then 12 in the placebo group, showing red. The vertical light blue line marks the baseline point. When the patients received the one-time treatment, average errors ALSFRS-R total scores for the two groups were comparable. Both groups had average scores of 38 at screening and 36 at baseline. Throughout the 24-week post-treatment follow-up period, there was essentially no difference in the ALSFRS-R total scores between the two groups. It is not shown on this graph, but there was also no significant difference between the two groups in respiratory function as measured by SVC, or in mass of strength. Overall, the efficacy findings were negative and showed no benefit of treatment with MSC-NTF.

The applicant then conducted exploratory subgroup analysis of rapid progressors and slow progressors. The applicant defined the rapid progressors as patients with at least two points decline in their ALSFRS-R total score from screening to baseline. Slow progressors were patients who experienced a smaller decline during that period. As shown in the graph on the left, rapid progressors in the MSC-NTF group appear to have performed slightly better than those in the placebo group. However, as shown in the graph on the right, slow progressors in the MSC-NTF group appear to have performed slightly worse than those in the placebo group. The applicant hypothesized that rapid progressors may be more responsive to MSC-NTF treatment. The Phase III study was designed based on this hypothesis, and it enrolled only rapid progressors.

Again, the Phase III study, BCT-002-US, was randomized, double blind, and placebo-controlled. The study included a screening period, followed by a 12-week run-in period, to identify rapid progressors. Eligible patients were then randomized at a one-to-one ratio to receive

either MSC-NTF or placebo. Patients that underwent bone marrow aspiration dropped down to obtain autologous mesenchymal stromal cells. Each patient was scheduled to receive three intracerebral injections spaced eight weeks apart of either MSC-NTF at a dose of 100 to 125 million cells per treatment or equal volume of placebo. Total study follow-up was 28 weeks after the first treatment.

Key eligibility criteria included diagnosis of definite, probable, laboratory-supported probable, or possible ALS. Symptom onset within two years, and the upright SVC of at least 65% of predicted. Mutational use was permitted, no prior stem cell therapy was allowed. In addition, to be eligible, a patient needed to have an ALSFRS-R total score of 25 or higher at screening and experienced a decline of at least 3 points during the 12-week growing period prior to randomization. A total of 263 patients were screened. 196 were randomized. 189 received at least one paid treatment and 144 patients completed the study. The intention to treat ITT population included all 196 randomized patients. The modified intention to treat mITT population was defined as patients who received at least one treatment. And have had at least three ALSFRS-R as far as our assessments. That is one at pre-treatment, one at baseline, and one at post-treatment. The mITT population included all 189 treated patients, 95 in the MSC-NTF group, and the 94 in the placebo group. The mITT population was used for all analyses of primary and key secondary efficacy endpoints. Demographics and the baseline disease characteristics were balanced between the MSC-NTF group and the placebo group in the mITT population.

The primary efficacy endpoint was proportional to responders. A responder was defined as a patient with at least 1.25 points per month improvement in the post-treatment linear regression slope compared to pre-treatment slope of ALSFRS-R total score. Patients not meeting

this criterion were considered as non-responders. Patients who died due to disease progression were also considered as non-responders. The key secondary efficacy endpoints were proportion of patients with 100% or greater improvement in the ALSFRS-R linear regression slope after treatment, change in ALSFRS-R total score from baseline to week 28, combined analysis of function and survival CAFS at week 28, change in SVC from baseline to week 28, tracheostomy-free survival, and survival.

Before going into the efficacy results, we would like to take a moment to discuss the primary efficacy endpoint. As you have heard this morning, the ALSFRS-R is an ordinal scale consisting of 12 items, covering four functional domains: bulbar, fine motor, gross motor, and respiratory. Each item is scored from zero, which is unable to perform, to four, which is normal function. The total score is the sum of the 12 item scores, and it ranges from zero to 48 with higher scores indicating better function. The primary efficacy endpoint of the Phase III study was based on comparing the ALSFRS-R linear regression slope before and after treatment. Modeling progression as a linear function, however, has significant limitations. As shown in the graph on the right, disease progression inspired by ALSFRS-R is not linear. The rate of disease progression varies among patients, as well as across different time periods of an individual patient. Such intervals of spontaneous stabilization or improvement make it difficult to interpret changes in the linear regression slope, especially within the limited time frame of a clinical study.

FDA and applicant did not reach agreement on the primary efficacy endpoint for the Phase III study. However, in reviewing the BLA, FDA assessed all primary and key secondary endpoints to determine whether the study demonstrated substantial evidence of effectiveness for MSC-NTF for the treatment of ALS. Those endpoints included overall survival and

tracheostomy-free survival, change in the ALSFRS-R total score from baseline to week 28, as we see CAFS, as well as change in the ALSFRS-R linear regression slope.

The Phase III study filled all its primary and key secondary efficacy endpoints. This table lists the efficacy findings for the mITT population. This is a basic table. The primary and some key secondary endpoint findings are bolded as examples. From top to bottom, responder rates were 32.6% for the MSC-NTF group and 27.7% for the placebo group, with an odds ratio of 1.33 and a p value of 0.45. Average ALSFRS-R change from baseline were minus 5.52 for the MSC-NTF group and the minus 5.88 for the placebo group. Slow vital capacity declined by 12.9% for the group and the 11.6% for the placebo group. We would like to emphasize that this is not a case where an investigational product demonstrates a clear, consistent, and favorable trend, but it just misses the bar for statistical significance. Rather, as shown here, for MSC-NTF, there is no such trend. Furthermore, all-cause mortality, shown in the bottom row, was much higher in MSC-NTF group, with ten deaths by week 28, compared to three deaths in the placebo group.

As shown in this graph, there was clear divergence in the Kaplan-Meier estimate of survival which favored the placebo group. That divergence started after the second treatment and continued to the end of the study. This difference in the Kaplan-Meier estimate of survival had a nominal p value of 0.04. The Phase III study did not include a long-term follow-up beyond 28 weeks. Patients do remain blinded to their treatment in the study. The applicant reported that there were 12 additional deaths in the MSC-NTF group and 15 additional deaths in the placebo group after study completion. But this information does not represent a comprehensive data regarding deaths following the study. Therefore, we can't draw any conclusions about the effect of MSC-NTF on long-term survival.

In the next couple of slides, I will provide a high-level overview of safety findings in the Phase III study. All patients experienced at least one adverse event. During the study, there were more deaths in the MSC-NTF group than in the placebo group. Overall, in the ITT population, that is, for all randomized patients, a total of 16 deaths were reported, ten in the MSC-NTF group and six in the placebo group. Two of the deaths in the placebo group occurred after randomization, but before the first treatment. As I mentioned, a total of 13 deaths occurred during the 28-week follow-up period. Additionally, one patient in the placebo group died after withdrawing from the study and outside of the protocol defined a 28-week follow-up period.

Respiratory failure was the most common treatment in emergent serious adverse event. While the incidents of this serious adverse event was low overall, it was higher in the MSC-NTF group than in the placebo group. In addition, MSC-NTF patients experienced a higher frequency of pain, such as back pain, musculoskeletal pain, and coccydynia, which would negatively impact the quality of life, especially considering that there was no treatment benefit. Muscle spasms and dysphagia also appeared to have occurred more frequently in the MSC-NTF group, which may suggest continued disease progression in MSC-NTF treated patients.

The applicant carried out planned exploratory subgroup analysis, looking at duration of symptom onset and the baseline ALSFRS-R total score threshold of 35. We would like to note that this threshold was chosen because it was the anticipated baseline mean for the Phase III study populations. And it was not intended to provide a standalone definition of disease stage or severity. Additional subgroup analysis, included Riluzole use, sex, and race. The applicant also conducted post hoc analysis as well as genetic and biomarker analysis. My colleagues will discuss this analysis in detail. I will now turn it over to Dr. Mary Lin.

Dr. Lin: Thanks, Dr. Liu. Good afternoon. My name is Xue Mary Lin. I'm the statistical reviewer of this BLA. I'm in the Office of Biostatistics and Pharmacovigilance at CBER. My presentation will focus on the statistical review of the efficacy data of the PIII three study, BCT-002-US.

Two key points of study BCT-002-US efficacy results. First, MSC-NTF showed no efficacy compared to placebo on primary and all key secondary endpoints in the overall population. Second, exploratory and post hoc subgroup analysis cannot provide substantial evidence of effectiveness.

The statistical analysis methods, the combined analysis of function and survival, CAFS score, was analyzed using ANCOVA, adjusting for five covariates, baseline ALSFRS-R score, duration from onset of symptoms to first treatment, site of onset, Riluzole, ALSFRS-R Slope Pretreatment. Change from baseline in ALSFRS-R at week 28 was analyzed using mixed effects, repeated measures, adjusting for the same covariates. Binary endpoints or analyzed using logistic regression, adjusting for the same covariates. In change from baseline SVC at week 28 was analyzed using the same method as change from baseline in ALSFRS-R. The two survival endpoints were analyzed using log rank tests and Cox model adjusting for the same covariants.

Other statistical considerations include analysis population. The primary analysis population was the mITT population. There were subjects randomized, treated, and had at least the three ALSFRS-R assessments prior to baseline, baseline, and post-treatment. To control the type one error rate, a sequential testing strategy would be used if the primary endpoint result is statistically significant, then the key secondary endpoints would be tested in a predetermined order. Of note, there was no alpha allocated to the subgroup of patients with baseline ALSFRS-R score greater than or equal to 35.

This table summarizes the efficacy results of the primary and all key secondary efficacy endpoints in the mITT population. These results collectively and consistently show the lack of efficacy of MSC-NTF over placebo for the primary endpoint of ALSFRS-R greater than or equal to 1.25 points improvement. In slope, 32.6% subject met this criterion in the MSC-NTF group and 27.7 in the placebo group. The odds ratio was 1.33 with 95% confidence interval being 0.63 to 2.8 with a p value of 0.45. From a statistical point of view, when the primary efficacy endpoint failed to show statistical significance, there was no alpha left to test the secondary efficacy endpoints. However, we reviewed the key secondary endpoints to evaluate the totality of data. Lack of efficacy also confirmed on all key secondary endpoints. For example, the percentage of subjects had a greater than or equal to 100% improvement in slope differed by only 0.1%. The ALSFRS-R changed from baseline at week 28, differed by only 0.37 between MSC-NTF group and the placebo. CAFS score differed by only three. Notably, more deaths occurred in the MSC-NTF treated group than the placebo group. 10.5% subjects died in the MSC-NTF group and three percent in the placebo group. The hazard ratio was 3.3 with 95% confidence interval 0.87 to 12.66.

This figure showed that the two study groups had a similar change from baseline, ALSFRS-R total score at all study visits. The Maximum Mean Square Mean Difference was achieved at week 12 visit with the mean difference at one point and at all other visits, including week 28. The mean difference was within half of a point.

MSC-NTF group appeared to have worse overall survival compared with the placebo group. The curve on the top colored red was the Kaplan-Meier curve for the placebo group. The curve on the bottom colored blue was for the MSC-NTF group. This figure suggests that subjects in the placebo group survived longer numerically than the MSC-NTF group.

MSC-NTF showed no efficacy compared to placebo on primary and all key secondary endpoints in the overall population. BCT-002-US was a failed study. The applicant then tried to rescue the failed study by exploring various subgroups. However, we reiterate the statistical principle that exploratory and post hoc subgroup analysis cannot provide substantial evidence of effectiveness to support regulatory approval because such analysis has a high risk of obtaining false positive results. They lack the control for multiple hypothesis testing and such analysis breaks randomization that may result in imbalance in measured and unmeasured baseline prognosis factors, which leads to confounding. Prespecification is the cornerstone of reliable regulatory evidence. Without a prespecified multiple hypothesis testing strategy, the subgroup analysis of patients with baseline ALSFRS-R score greater than or equal to 35 is an exploratory analysis. In the presence of an overall negative trial result, this subgroup analysis may be used to generate a hypothesis for another trial. However, they cannot be used to rescue the trial because of a large chance of a false positive finding.

The applicant's post hoc exploratory subgroup analysis focused on floor effect. The applicant argued that once physical function is lost and the value of an item reaches zero, further loss cannot be measured even as the patient's condition further deteriorates. ALSFRS-R cannot measure further decline once items reach zero, making a treatment effect difficult to measure in participants with low ratings. A floor effect could appear as an improvement or slowing of decline, and thereby be misclassified as a clinical response. The applicant conjectured that lack of efficacy in overall population was due to inability to detect efficacy in the subgroup impacted by floor effect.

To support their conjecture, the applicant conducted a post hoc subgroup analysis to identify patients not impacted by floor effect by three definitions. Definition one, total score

threshold baseline ALSFRS-R total score greater than 25. This subgroup has a sample size of 145. Definition two, items level threshold. At least two of the six items in fine motor and gross motor scales of ALSFRS-R with baseline value greater than or equal to two. This subgroup has a sample size of 159. And the third definition, no ALSFRS-R item with a value of 0 at baseline with a sample size of 106. FDA will refer to each subgroup as no floor effect subgroup. And its respective complement as with floor effects subgroup.

FDA considers the applicant's floor effect analysis post hoc spurious findings. Extensive subgroup exploration is always likely to find both positive and negative results that are not real signals or real patterns, but spurious findings due to random chance or selection bias. In addition, though a floor effect can occur, FDA did not observe an actual floor effect in the with floor effect subgroups identified by applicant. If floor effects were present, with floor effect subgroups would have shown lower bound for ALSFRS-R total score post-baseline, preventing much further decline. But applicants with floor effect subgroups had a drastically steeper decline in ALSFRS-R total score from baseline and no floor effect subgroups. We don't think extensive subgroup exploration will yield meaningful results. The figures in the next two slides are for illustration purposes only.

This figure showed ALSFRS-R total score change from baseline by treatment group and subgroup type, with or without floor. No floor was defined as baseline ALSFRS-R total score greater than 25. Red coded for placebo-treated and blue coded for MSC-NTF treated, the solid line is no floor subgroup, the dashed line represents floor effect subgroups. It appears that while the MSC-NTF showed a positive treating effect over placebo for no floor effect subgroup, as the two solid lines indicate. The treatment effects seem to be flipped for the floor effect subgroups as the two dashed lines indicate. This is just an illustration that when you explore subgroups

extensively, both positive and negative results can emerge, but they're not real signals or real pattern, but spurious findings. In addition, subjects in the with floor effects subgroup who were treated with MSC-NTF had a steeper decline in ALSFRS-R total score from baseline than the rest of the subgroups. If there were a floor effect in this applicant, identifying the floor effects subgroup, the ALSFRS-R total score post baseline, would have been bounded by a floor. Which would have prevented a floor from much further decline, which is in direct contrast with what we have seen in this figure.

We noticed a similar pattern in another floor effect definition. In this figure, no floor effect was defined as item level had no value zero at baseline. We observed the same pattern. That is while the MSC-NTF showed a positive treatment effect over placebo for no floor effect subgroup as the solid lines indicate. The treatment effect was flipped for the floor effect group as the dashed line indicates, the applicant this morning showed this figure, arguing that the finding of worse result for MSC-NTF than placebo in the floor effect subgroup was due to an imbalance in the number of placebo patients who plateaued. Saying that more placebo patients plateaued is just another way of saying that more MSC-NTF patients declined very quickly. The applicant's argument is tantamount to stating that because the MSC-NTF group declined more steeply compared to the placebo group, it was not possible to demonstrate a relative improvement compared to the placebo group. The FDA's belief is that this worsening is likely an artifact of selection bias. The applicant is focusing on the no floor effects subgroup because the data appear favorable for MSC-NTF in this group. Unfavorable data in the complement floor effect subgroup is a natural consequence of this selection. In fact, both subgroup findings are very likely to be spurious. Given all the above on post hoc analysis of floor effect, we conclude that lack of

efficacy in the overall study population cannot be explained by inability to detect efficacy in subgroup impacted by floor effect.

The applicant has spoken often today of the totality of evidence, including in Dr. Wei's presentation about robustness and consistency. But in their presentation totality and consistency of efficacy only apply to the exploratory subgroup analysis. True totality of evidence would include a failure on primary and all key secondary endpoints in the overall study population plus suggestion of survival disadvantage. This analysis is subject to the same inflated chance of positive findings as the applicant's other exploratory and post hoc subgroup analysis with additional multiple testing issues due to further exploration. The p values are uninterpretable. The permutation test does not protect from uncontrolled type one error inflation associated with post hoc or exploratory testing in any way. Methodological papers cited by the applicant do not propose this method be applied to post hoc or exploratory subgroups.

To summarize findings from statistical review of the efficacy data of the study BCT-002-US, MSC-NTF showed no efficacy compared to placebo on primary and all key secondary endpoints in the overall population. Exploratory and post hoc subgroup analysis cannot provide substantial evidence of effectiveness. I will now turn it over to my colleague, clinical pharmacology reviewer, Dr. Wang. Thank you.

Dr. Wang: Thank you, Dr. Lin. Good afternoon, everyone. My name is Xiaofei Wang, clinical pharmacology reviewer for this application. I work in the Office of Clinical Evaluation, Office of Therapeutic Products, CBER. Here, I will present the collaborative work among Dr. Vishnu Sharma, pharmacometrics consult reviewer from the Office of Clinical Pharmacology, CDER. Dr. Thomas Zhou, Statistical Reviewer from the Office of Biostatistics and Pharmacovigilance CBER, and me.

MSC-NTF is intended to provide support for motor neurons in the patient through the secretion of neurotrophic factors within cerebral spinal fluid, CSF. To support its application, the applicant assessed multiple biomarkers in CSF in its Phase III study. Study BCT-002-US in this study MSC-NTF all placebo was administered intrathecally at week 0, 8, and 16. Cerebrospinal fluid samples were collected at baseline and at week 2, 4, 8, 12, 16, and 20 for biomarker analysis. As shown in this slide, a panel of 45 biomarkers in four categories were analyzed. Neuroinflammation biomarkers, including anti-inflammatory and inflammatory biomarkers, neurodegeneration biomarkers, neuroprotection biomarkers, and others. The applicant performed numerous exploratory analyses, including post hoc analysis, to evaluate the relationship between the selected biomarkers and clinical efficacy outcomes. It is noticed that in this submission, there was a large amount of missing data, 50% or more, at week 20 for all biomarkers.

Based on the numerous exploratory analysis the applicant chose to emphasize on the following biomarkers that are potentially associated with ALS disease progression. Neurofilament light chain, NfL, and neurodegeneration biomarker to neuroprotection biomarkers, Galectin-1, and vascular endocilia growth factor eight, VEGF-8. One anti-inflammatory biomarker latency-associated peptide LAP or TGF beta-1, and the one pro-inflammatory biomarker, monocyte chemoattractant protein one, MCP-1. This slide shows the longitudinal percent changes of the selected CSF biomarkers. In the plot, the blue color represents MSC-NTF treatment group, and the gray color represents the placebo group. Focusing on the neurofilament light chain, it is one of the neurofilament proteins that are highly expressed in myelinated axons. It is a neurodegeneration biomarker and as a consequence of axonal damage, elevated levels of NfL in CSF and blood are found in a variety of neurological disorders, including ALS. As shown in the left graph, similar levels of NfL was seen in patients

treated with MSC-NTF or placebo. Of note, about 50% data was missing at B20 for NfL, similar to other biomarkers. The graphs on the right show the longitudinal profiles of other four biomarkers. Galectin-1, VEGF-8, LAP, and MCP-1. Where all the changes in these biomarkers were observed in the treatment group as compared to the placebo group. It is important to evaluate the clinical relevance of these biomarker changes

These slides show the relationship between NfL changes at week 20 and ALSFRS-R total score change at week 28. In the study BCT-002-US, this helps us to understand the clinical evaluated relevance of these biomarker changes. The blue color represents the MSC-NTF treatment group, and the placebo group data is shown in gray color. As we mentioned in the previous slide, as a consequence of axonal damage, elevated levels of NfL in CSF and blood are found in ALS, a reduction in NfL is expected to be associated with reduction in clinical decline of ALSFRS-R total score. However, in the current data set, patients experiencing greater loss of function appears to have a higher reduction of NfL, the opposite of what would be expected. This observation could be influenced by about 50% missing NfL data at week 20, and relatively overall small changes in CSF NfL in the MSC-NTF treatment group.

This slide shows the relationship between NfL changes at week 20 and ALSFRS-R total score change at week 28 in subgroups based on various floor effect definitions proposed by the applicant. The left graph shows the relationship in patients not impacted by floor impact effect based on the applicant-proposed floor effect definition one patients with baseline ALSFRS-R total score more than 25. The right graph shows the relationship in patients not impacted by the floor effect based on the applicant proposed floor effect definition three. Patients with all baseline ALSFRS-R item scores above 0. In both subgroups, we see the same trend as the previous slide. Patients experiencing greater loss of function appeared to have higher reduction

of NfL, the opposite of what would be expected. Of note, these findings could be due to 50% missing NfL data at week 20, and relatively overall small changes in CSF NfL levels in the treatment group. In the setting of negative Phase III trial findings. It does not appear that these correlation analyses provided direct evidence on treatment effect through changes in CSF NfL.

In April 2023, FDA granted accelerated approval of Tofersen for the treatment of Superoxide Dismutase one, SOD-1 ALS based on a reduction of NfL. In this application the applicant has suggested as one of the mechanistic pathways of MSC-NTF therapy. This slide shows the longitudinal percent changes of iNfL the two applications. As shown in the left graph, CSF NfL levels were similar between MSC-NTF treatment and placebo groups in this application. At week 20, MSC-NTF treatment resulted in about nine percent reduction in CSF NfL as compared to the placebo group. The right graph shows plasma NfL levels over time in the application of Tofersen. In study 101, part C, treatment of Tofersen induced the sustain substantial reduction of plasma NfL levels from week eight to week 28. Specifically, at week 28 Tofersen treatment resulted in 67% reduction of plasma NfL as compared to placebo group. Study 102 was an open-label extension study, which confirmed the finding of plasma NfL reduction observed in study 101, part C.

We have also evaluated the clinical relevance of four other biomarker changes including Galectin-1, LAP, MAP-1 and VEGF-8 and the slide shows the relationship between these biomarker's changes at week 20 and ALSFRS-R total score change at week 28, MSC-NTF Treatment Group data is shown in blue color and placebo group is in gray color for all four biomarkers. There's no evident association between biomarkers percent change from baseline to week 20, and the change in ALSFRS-R total score from baseline to study completion at week 28.

These findings suggested that changes in these biomarkers may not predict the changes in ALSFRS-R total score.

In summary, in our biomarker analysis, we noticed a large amount of missing data for biomarker measurements at week 20, the last biomarker sampling timepoint. A large amount of missing data could compromise the validity of biomarker analysis. and lead to overestimation of the correlation between the biomarkers and efficacy endpoints. There's no clear association between the change of selected possible ALS progression-related biomarkers and clinical end benefit. For NfL, a biomarker for neurodegeneration, we observed an opposite-to-expected association. Patients experiencing greater loss of function, which mattered by change of ALSFRS-R total score from baseline to week 28 appears to have more reduction of CSF NfL. For other possible ALS progression-related biomarkers, Galectin-1, LAP, MCP-1, and VEFG-8. We did not see any evident association between the percent change from baseline to week 20 and the change in ALSFRS-R total score from baseline to study completion at week 28.

We also have some statistical concerns for the biomarker analysis. First of all, the applicant's numerous biomarker analyses were proposed without multiplicity adjustment or formal hypothesis testing. Because there was no overall type one error rate control, any nominal statistical significance claim could be due to chance alone. The results from this analysis should be considered as exploratory. In addition, the applicant conducted multiple post hoc analyses after the data were unblinded. These post hoc analyses in general have a high chance of false positive findings, which are favorable to MSC-NTF treatment.

In summary, the available biomarker data do not indicate persuasive association between any of the assessed biomarker changes and the clinical benefit. The available biomarker data do not provide supportive evidence of effectiveness of MSC-NTF. The potential maximum of action

of MSC-NTF may involve multiple pathways. The efficacy assessment of MSC-NTF should be based on the totality of evidence. I would like to hand it over to my colleague, Dr. Gumei Liu, the clinical reviewer, to continue our assessment for MSC-NTF. Thank you.

Dr. Liu: Alright, thank you, Dr. Wang. This is Gumei Liu again. In this final portion of our presentation, I will discuss FDA's assessment of the totality of data for MSC-NTF.

As discussed, we reviewed the efficacy findings from the Phase II and Phase III studies. The Phase II study was randomized, double blind, and placebo-controlled. It had a different treatment regimen but provided additional insights regarding the efficacy of MSC-NTF and as shown in this graph here, there was no difference in errors of ALSFRS-R total scores between MSC-NTF and the placebo group. We would also like to note that patients enrolled in the Phase II study had the less advanced disease than patients in the Phase III study, as measured by ALSFRS-R scores at baseline.

You have seen this graph in the morning, but without the Phase II study population. We would like to point out that while the Phase III study population had a baseline mean of approximately 31, the Phase II study population had a baseline mean of 36. And then there was no clinical benefit with MSC-NTF treatment in the Phase II study. More importantly, we would like to note that the determination of an appropriate ALS population to a treatment does not solely depend on baseline ALSFRS-R scores. For example, Tofersen, based on its mechanism of action, is intended to treat ALS patients with SOD-1 mutations, regardless of baseline errors of ALSFRS-R scores. For MSC-NTF based on the proposed mechanism of action, it is unclear whether it would specifically benefit a subpopulation. For example, patients with mild to moderate disease as proposed by the applicant.

The Phase III study evaluated the efficacy of repeated intrathecal administration of MSC-NTF. This study was also negative. In addition, survival was worse in the MSC-NTF group compared to the placebo group, while the relatedness of the deaths to the product was not clear. The higher mortality is consistent with the lack of treatment benefit for MSC-NTF.

The applicant's claim of effectiveness relies on subgroup analysis. However, with breaking of randomization, subgroup analyses are subject to bias and incidental findings, and it must always be interpreted with caution. Even when predefined such analyses are not reliable for overturning negative efficacy results in the overall study population and concluding that a treatment works in a subpopulation. For example, a higher responder rate was reported in males treated with MSC-NTF, which was a predefined subgroup analysis. This finding was deemed spurious by the applicant. And we agree, incidental findings of subgroup analysis should not be interpreted on its own. Factors such as mechanism of action and disease characteristics should be considered by interpreting such results. Based on current understanding of the product and the disease, we cannot conclude that the treatment preferentially benefits a particular sex. This finding warrants further investigation. And we would like to emphasize that the same principle and caution should be applied to all subgroup analyses, be it subgroups based on demographics, genetics, disease severity, or any other baseline characteristics. For example, the applicant discussed in the morning session findings in the subgroup with baseline errors ALSFRS-R score of 35 and higher. This subgroup accounts for only one-third of the mITT population. Findings of this subgroup are subject to the same limitations as any other subgroup, therefore, need to be interpreted with caution. That is not to say that the subgroup analyses do not have value. Findings from exploratory subgroup analysis can be used to generate hypotheses to potentially identify subpopulations for targeted follow-up studies.

There has been considerable discussion about floor effects. When the Phase III study did not show efficacy in the overall study population, the applicant conducted post hoc subgroup analysis, which excluded patients thought to be affected by a floor effect. The applicant proposed that the analysis in the no floor effect subgroups support efficacy of MSC-NTF for the treatment of ALS. The question, however, is whether a floor effect indeed was responsible for the lack of efficacy seen in the Phase III study. As discussed, FDA did not see evidence of a floor effect in the Phase III study. The applicant explored three different definitions of floor effect. The graph on the right uses baseline ALSFRS-R total score threshold of 25 as an example. Trajectories of the placebo groups shown here in red are superimposed, which suggests absence of an actual floor effect. Furthermore, the MSC-NTF with floor effect group, which is the dashed blue line, shows a steady and a larger decline compared to the corresponding placebo subgroup. This steep decline cannot be simply explained by a floor effect. Therefore, while the ALSFRS-R skill itself may be subject to a floor effect, the lack of efficacy seen in this Phase III study is unlikely due to a floor effect.

The applicant's biomarker analyses were exploratory and did not support clinical benefit. In the mITT population, greater reduction of neurofilament light chain in MSC-NTF was associated with worse clinical outcome, the opposite of what would be expected. No clear association was observed between changes in the selected biomarkers such as VEGF and the clinical benefit.

In summary, two randomized, double blind, placebo-controlled studies failed to show efficacy for MSC-NTF. Survival data from the Phase III study were limited and unfavorable. The subgroup analyses can only be considered exploratory. The lack of efficacy in the studies cannot be explained by a floor effect. Biomarker analyses are also exploratory. And the correlation

analyses do not support clinical benefit. Finally, product characterization and the manufacturer controls are inadequate.

In conclusion, the totality of data submitted in this BLA does not demonstrate substantial evidence of effectiveness of MSC-NTF for the treatment of ALS or the subgroup of ALS. New, adequate, and well-controlled clinical studies would be needed to provide substantial evidence of effectiveness for the treatment of patients with ALS or for the treatment of patients with mild to moderate ALS.

And that concludes the FDA review team's presentation. We would like to thank everyone who contributed to this AC and thank you all for your attention. Back to you, Dr. Ahsan.

Q & A

Dr. Ahsan: Great. Thank you very much. I appreciate all the presentations by the FDA. They were very informative. At this point, we have a time for asking questions. I know that we had queued some questions up that were for the sponsor, but we will still put that aside. This is our time to ask questions of the FDA presenters. So, if committee members can raise their hand if they have questions, and then we can go through. Dr. Alexander, if you could put yourself on camera and unmute yourself, please.

Dr. Alexander: Thank you. The presentation was great and very informative. I think the FDA's December 2019 guidance does a nice job of spelling out what substantial evidence means and how the FDA determines that. And there's some discussion in there about the importance of replication. There's also of note that having two trials of different designs or conducts is valuable so as to hedge against biases that may otherwise be introduced in both trials. So, if a decision was made not to approve the product at this time, if that was the case, what would be the main recommendations you would have about the design of another trial? Another pivotal efficacy trial that would depart from the design that was used in the trial that we've just reviewed.

Dr. Witten: This is Celia Witten, and I'll make a general comment and then see if Lei Xu wants to add anything. But if that happens, first of all, that's a question that we are hoping to get some input from you all, depending on what your recommendation is. So, we would take that into account. But also, it's something where we would take a step back and work with the sponsor, like we would with any sponsor to try to develop their product. But let me ask, Lei, do you have anything to add?

Dr. Lei Thank you, Celia. I don't think I have much to add. I think in the 2019 substantial evidence of effectiveness guidance, we did have the option of either two adequate and well-controlled studies or one adequate and well-controlled study plus confirmatory evidence, which could come from different sources as outlined in that guidance document. But as Celia mentioned, we're willing to work with the applicant to come to a design if they intended to continue the development of the product for this indication. Thank you.

Dr. Alexander: Thank you.

Dr. Ahsan: Great. Thank you. If we could go to the next question, Dr. Fischbeck. If you could go on camera and unmute yourself, please.

Dr. Fischbeck: Yeah, my questions were more aimed at the sponsor, but they were also addressed by the FDA and so, I think they're worth reiterating. The idea of post hoc analysis. So, I'm not a statistician, but statisticians that I highly respect have said not to do, don't go there, don't do it. And I wonder, I think your point is well taken that it's not used to support efficacy as the sponsor proposed here but may generate some interesting hypotheses for further testing or designed for future trials such as limiting the ALSFRS score to over 35, for example. But I'm wondering if I'm being too harsh on postdoc all these years or if it's warranted to say that it's not something to be used for efficacy. Is that a fair statement or not? That's my question.

Dr. Ahsan: I think, Dr. Fishbeck, that might be actually something to leave for the discussion for the committee, unless you thought that there was one particular person on the FDA speaker list that would—

Dr. Fischbeck: Yeah, I was just thinking of Dr. Lin who talked about the statistical analysis, but if she has—

Dr. Ahsan: Okay. If she has a comment, that would be great.

Dr. Lin: Hi. Thanks, Dr Fischbeck. Thanks for your question. I think post hoc analysis and can provide supportive evidence to reinforce the treatment in effective evaluation, if there's a real treatment, in fact. But I think in this trial, it's totally different. I think the sponsor of the applicant's evidence of effectiveness comes solely from exploratory and post hoc analysis. And I don't think that will be very convincing for us.

Dr. Fischbeck: I guess another related statistical question is about the floor effect. I was struck by that. I'm not used to seeing floor effects based on subtest analysis. I think it was something to look for in the whole subtest together as you did. Is there a reference to this kind of approach? Or do you know of any historical support for looking at far-effect and subtests like this? Again, that was a question for the sponsor. But if you have any input, I would appreciate it.

Dr. Lin: Yeah, I think the floor effect is a very interesting effect that the sponsor dug really deep into it and try to explain the lack of advocacy and overpopulation that they think they. It's because of the lack of inability to detect efficacy in the so-called for floor effect subgroup. But like you said, there's limited literature the about the floor effect and also in other FDA-approved drugs that the floor effect was not very focused.

Dr. Fischbeck: Thanks.

Dr. Ahsan: Great. If we can leave the questions for the sponsors, we will try to carve out time for that before the discussion. So, these are still questions directed to the FDA speakers. Andrew Buckley, if you would like to go on camera and unmute yourself.

Mr. Buckley: Good afternoon. My question is in regard to the missing week 20 data. I was curious to know whether or not the sponsor offered any response to that missing data. Was it ever provided or was there ever any reasonable explanation as to why not?

Dr. Witten: I think there might be a question for the sponsor as to the missing data, but I don't know. Xiaofei, you have a response to that missing data. Otherwise, I'd ask the sponsor.

Dr. Lin: Yes, thanks. I would like to defer to the sponsor to address the question. Thank you.

Dr. Ahsan: Okay, we'll be sure to bring that up at the when we're asking our questions or continuing our questions for the sponsor. Dr. Lynn Raymond, if you would like to unmute yourself.

Dr. Raymond: Hi, thanks. That was really helpful, both the written material and those presentations. So, my question is about the biomanufacturing and quality control. So, I guess for Dr. Finn, I heard reference to how the data available on release of these neurotrophic factors from the cells for different batches, maybe even from the same patient did not necessarily correlate with the CSF results on different biomarkers, but we never saw any data on release factors to see that lots actually did that or how variable that was. Did you have that data or does the sponsor have it?

Dr. Finn: Yeah, that data exists, but unfortunately manufacturing information is typically considered trade secrets, so if the sponsor wants to share that data, but we do look carefully at that for all types of biological products. How consistent is the manufacturing? What levels are

they cutting off? What are they deciding is adequate quality to assure that every patient gets a product lot that has at least the potential to have an effect? So, we look at that variability, but we also look then at is there any correlation? There doesn't have to be sometimes there's not. That's frustrating, but that occurs. But that does make it more challenging both to have an idea of what's predictive of what would be efficacious in vivo as well as it's challenging to say, are their specifications adequate.

Dr. Raymond: Right.

Dr. Finn: It's just you just have to rely more on scientific and mechanism of action.

Dr. Raymond: I just wanted to comment that the only response the sponsor had when someone else asked a question about the product itself was about the number of cells. That was carefully controlled, but we don't know that those cells had any enhanced secretion of neurotrophic factors that I heard.

Dr. Finn: One follow-up on that is that Dr. Wendebank did mention that they, in their preclinical studies, looked at estimation of how much the cells would need to have a cumulative effect in vivo.

Dr. Raymond: Yes.

Dr. Finn: And we've looked at the calculations, our own kind of calculate that wasn't in the BLA, but we've done our own calculations. And that doesn't seem supportive.

Dr. Raymond: Okay. Thank you.

Dr. Ahsan: Thank you. I'm sure when we ask questions of the sponsors, we can give them an opportunity if there's anything related to the product that they want to share that they're welcome to do so then. Thank you, Dr. Finn. Dr. Michael Gold. If you could go on camera, thank you.

Dr. Gold: It's quick. So, one quick comment and then a question. In terms of floor effects and for folks who work in Alzheimer's disease the 8S COGS score, which has been a gold standard, has a longstanding problem with floor effects and that hasn't stopped from drugs being approved with it or being used in clinical trials. But it's a follow-up to the question about the CMC. I'm trying to understand where in terms of do the cells actually produce what they're supposed to produce? Because it's not a single peptide that's being produced. It's a family or set of neurotrophic factors. That's what I got to understand. And so, I'm trying to understand whether, from subject to subject, because the cells are autologous, are they expected to produce the same amount of this cocktail of neurotrophic factors? And assuming that there's a single bone marrow harvest that has a limited yield. Is there evidence that if you have to do a second or third bone marrow aspiration, and you're actually going to treat patients with materials derived from a second or third aspiration that you can actually get the same consistency in terms of products. I'm trying to understand, and I know that despite that it's possible, but also gets to CMC and clinical pharmacology on the FDA side. Has the FDA developed a position on whether there's actually evidence of target engagement, so to speak?

Dr. Witten: This is Celia, that's a really great question and I'm going to ask Tom to comment on it. But one part of it is the question of what is the mechanism of action proposed by the sponsor? And I think Tom talked about that a little bit in his presentation but may have something additional to say. Tom.

Dr. Finn: Yeah, thank you. So that's a great question. And there's no exact clear answer. So, it depends on what the underlying mechanisms of action are. Our understanding from the BLA from, early development under IND was what is particularly special about this product is that the cells are cultured under conditions where they will increase the amount of neurotrophic factors

that they normally produce. Hopefully at levels that would be beneficial. Exactly which factors they produce is not entirely clear. The sponsor has looked at several, but not consistently during clinical development or for the commercial manufacturing. And then that's only a subset of all the different known motor neuron trophic factors like CNTF and GDNF and other things, NT3, NT4. And then also they're mentioning a dual mechanism where neuroimmunomodulation might play as equal of a role, and that could be through secretion of anti-inflammatory cytokines such as TGF-beta. But that's not measured for product release, and it's not measured as part of product characterization. So, we don't actually know what the level of variation there is in the milieu of factors that could be secreted. How much it varies by different product lots and how consistent that is even from the same frozen intermediate. So, one bone marrow collection is used to produce one frozen intermediate from which three product lots are generated for patient treatment. But there's variation in trophic factor levels from that same frozen intermediate. Sometimes it's very consistent. Sometimes it's not.

Also, the dose that's generated. It's 100-125 million cells. I believe the intention is to always produce 125 million. But in a quarter of the cases, it was not. It's not clear whether a 100 million dose is actually efficacious. We're still looking into that, but there's very limited data on that as well. So, these are the kind of concerns we have about manufacturing consistency to make sure that once you do define what would be efficacious, is the manufacturing consistent and will it stay consistent as a commercial product?

Dr. Ahsan: Great. Thank you very much. Just, a note out to the sponsor that after this series of questions to the FDA, we will be allowing a few more follow-ups to the sponsor. So, if you do want to prepare anything related to CMC now would be your chance to start doing that. Dr. Rajiv Ratan.

Dr. Ratan: Yes. As you likely all know, growth factors can have deleterious effects if they bind to different receptors, inducing death or even inducing pain. So. my question was, in that analysis of side effects where you're seeing a dramatic increase in pain manifestations. Is that a statistically significant side effect? And could that be an indication of a growth factor-related adverse effect? I don't know if NGF is being actually measured.

Dr. Witten: That's a good question. I'm not sure who might be able to answer it, and the sponsor might have some comments on it too. But, Gumei do you have a comment on that question?

Dr. Liu: Sure, yeah. At least for back pain, and it is a significant increase in the MSC-NTF treated patients, whether or not it is related to the neurotrophic factor, that part is unclear. However, other MSC trials with intrathecal injections have reported a similar back pain, especially with higher dose. That actually was a dose-limiting factor for a lot of patients.

Dr. Ahsan: Very good. Thank you very much. Dr Shah.

Dr. Shah: Hi. So, this is a CMC-related question. What I'm understanding is that we have some theories and hypotheses about why these cells may work. But we don't really know. We don't know whether the NTF or the growth factor support is more predominant in terms of exuding an effect or there's an immunomodulatory. So, my question for the FDA is that as you think about what is the release, not even the release criteria, but what are the factors you need to be able to move this? What exactly are you looking for? Because I don't think that we really understand the mechanism of action, which makes it really hard to know what you're targeting.

Dr. Witten: In order to answer that question, because generally, that's something we would expect to hear from the sponsor what their product is. What are the critical attributes that will make the product effective? How they're going to make sure they achieve them in the product

and how that relates to product effectiveness. So, the sponsor would need to explain that and that relationship, but I don't want to overstep this, so let me ask Tom Finn if you have anything to add to that or modify what I said.

Dr. Finn: Thanks, Celia. No, that is exactly right. It is really up to the sponsor, the applicant to, especially early in development, decide on what they think is really important. And that could get modified as they do clinical studies. Biomarker analysis, they might decide that, for example, immunomodulation plays a more important role than neurotrophic factors or vice versa. So, it's up to them to decide and continually to update the product and specifications and the manufacturing process to align it so that the product hopefully does what you want it to do. Now, it is challenging if you don't know the mechanism of action, and it is challenging if you don't know all the factors that are being secreted and stuff. And in this case, we don't really know exactly what the fate of the cells are. Dr. Snyder talked this morning a lot, gave a lot of great examples of really powerful benefits you can have in animal models, various disease animal models. But in many cases, the cells had to persist and they had to integrate. We don't know if that's occurring for this particular product. So that would affect not only what properties they would have to have, but how it has to function in vivo, how long it has to persist. Does it have to integrate or not? Those kinds of studies are best answered with preclinical studies, but for this particular product there weren't much in the way of preclinical studies supporting how the product actually works and what's important.

Dr. Shah: And the criteria were not sufficient. Is that what I'm hearing? That were used to be able to move this forward.

Dr. Finn: That is one concern. Yes, this product’s specifications are a review concern. Yes.

Dr. Ahsan: Okay, in the interest of time, if we can stay direct on the question and direct on the answers, that'd be helpful where I don't want us to go too long in the day. So, Dr. Tuszynski, if you could move forward, please.

Dr. Tuszynski: All right. This is a question regarding the VEGF data, probably directed through Dr. Finn. The FDA presented the totality of the growth factor data a little differently than the company. The company was focusing, for example, with the VEGF data on two weeks after the first injection, and the FDA presented the composite data across all collection timepoints. Can you tell me why the FDA did that? And what the FDA's interpretation is of the two-week VEGF data, which does show an increase and then much less elevation following that timepoint, because I was wondering whether that indicates some early response being seen at two weeks. And then if you look at all time points together, that's washed out. So, do you have any thoughts on that?

Dr. Finn: Yeah, I think it would be helpful. There are many ways of displaying the data. And in fact, we struggled to find the best representative way of looking and analyzing the data. If I could have backup slide number 48, please. I think that might present it in a better way. That kind of illustrates the level of variation. So, this is looking at the various time points. So, in blue are the bars associated with the treatment arm. These are the CSF samples from those patients. And in red is the placebo arm, those patients. Not every patient had CSF samples collected, and as was pointed out before, there is a fair amount of missing data as well. But the sponsor does point out that at two weeks, they did see a peak, and that is interesting. What is challenging, though, is to look at the other timepoints, because you will notice that two weeks in this case is two weeks after the first treatment. The next treatment is eight weeks, so a two-week post-treatment would be ten weeks. That doesn't exist, so we don't know if there was a peak at ten

weeks, and also at eighteen weeks, or if it was just consistently low. You can see, though, with repeated treatments, it doesn't stay elevated. We don't want to overinterpret this data, but it suggests that the cells don't stick around for a long time. The sponsor does refer to some preclinical animal studies done by other groups with MSCs and various animal models like Nerve Crush, Parkinson's model, SOD models, and cells persisting for different levels of time. But there's a difference between saying you can find cells, some cells later versus the type of question I believe Dr. Wu asked this morning. If you put 100 cells in, how many do you see at a later time point? And the answer typically is, with MSCs and various studies, they don't persist for very long.

Dr. Tuszynski: Thank you.

Dr. Finn: Sure.

Dr. Ahsan: Great. And then last Dr. Li, if you could ask your question.

Dr. Li: I think we heard throughout the presentation the applicants emphasize quite a bit on the floor effect. And on the other hand, the FDA team emphasized quite a bit of increased death rate in the treated arm. And in my mind, the death rate would be less susceptible from the effect of floor effect. And I’m wondering if the team can elaborate on this issue, because I think this is a very critical one.

Dr. Witten: That's a good question. So, you're asking whether the death effect would be less susceptible to a floor effect? Is that what you're saying?

Dr. Li: Yes. In other words, the death rate itself is independent of the effect from the floor effect.

Dr. Witten: Right.

Dr. Li: Which is a critical one because that is something that the applicant has emphasized, right?

Dr. Witten: Yes. Okay. I understand the question and that's a good question. I'm wondering whether Mary Lin can respond to that.

Dr. Lin: Thanks Dr. Li. So, you raised a very good point. So, death itself is not impacted by the floor effect. If the patient deteriorated and continually, unfortunately, they died. So, I think as you pointed out the floor effect were not impacted. The death rate will not be impacted by the floor effect. So, I think it's looking at deaths we, we can see that the MSC-NTF group they have a higher death rate than placebo group. Thank you.

Dr. Ahsan: Okay, thank you very much. I think that's all the questions that I see that were raised specifically towards the FDA. As we try to catch up with some other items, I ask that those that I have listed as to whether or not that had questions for the sponsor at the end of their session, if you still have your question, please raise your hand because we are very tight on time today. And I want to make sure that we get to the questions and the responses and the understanding that we need. So, Dr. Liem, you were first before and you are here now with your question. If you want to get on camera and unmute yourself, that would be great.

Dr. Liem: Yeah, thank you very much. So, my question actually has to do with the fact that the sponsor is now asking for only mild and moderate ALS approval. And I was wondering about the biomarkers for the participants who had the ALSFRS scores of greater than 35. They just didn't separate that out in their presentations. Is there anything different that they see with that group?

Dr. Lindbergh: Thank you. And I was tracking all of the questions that were being asked during the FDA discussion. If after I respond to this question, you would like me just to run through them quickly. So, first I'm going to define, I'm going to answer a question from earlier that we hadn't defined mild and moderate. And then I'm going to respond to your question about the

biomarker data in the mild. So, we look at mild ALS as being above 35 so in the similar to the pre-specified group and the moderate being about 25. So, we're really looking across a set of participants that are earlier in their disease course and are in the first half of the scale. The biomarker data we have specifically analyzed the biomarkers that were shown here. And looked at the above 35 and we see the same magnitude of effects in terms of differences improvements from neuron compared to placebo across biomarkers and very consistent effects in that subgroup. And of course, we see changes across all participants in the trial on our biomarker data.

Dr. Liem: Okay, thank you.

Dr. Ahsan: Great. Dr Lindbergh, I'll allow you to answer the amorphous questions at the end. I've tagged a few of them as well. But while we're on this topic, could you define, because the indication changed just on Friday, and it's not in the written documents, can you define what mild to moderate ALS will be?

Dr. Lindbergh: Yes. We're looking at mild ALS as above 35 and moderate being above 25. So, really mild to moderate being in the upper half of the ALS functional rating scale.

Dr. Ahsan: So, while you stratified the data with a focus above 35, you are intending to include those above 25?

Dr. Lindbergh: Yes, that is correct. We have evidence, strong evidence in these participants, which I can share more of, time permitting. I would like to show some of the totality of evidence and answer questions from the FDA. Ask about the totality of evidence and it not only being present in the above 35 group. In fact, as Dr. Wei presented, as we increase the sample size, the strength of statistical evidence, as well as this methodology that Dr. Wei presented on with the totality of evidence becomes stronger and stronger. So, I'll show the above 25 group.

Dr. Ahsan: Actually, if I can ask you to hold, we have a series—

Dr. Lindbergh: Okay. Sure.

Dr. Ahsan: —of questions and then we can come back to that. Andrew Buckley, if you could turn on your camera and unmute. That would be great.

Mr. Buckley: Thank you. My question is, what is your position regarding the missing week 20 data that's been referenced and the overall integrity of the study results?

Dr. Lindbergh: Yeah, so the missing data that we've been talking about is only specific to the biomarker data. So, as the pandemic was progressing. Hospital policy did not permit participants to keep coming in if there was a non-intervention visit and week 20 was not a visit where treatment was given. So, we have missing samples at that week 20 where the week before you have 75% of the samples that were collected. In fact, if you look at all seven time points where we were to collect the CSF samples, first, 98% of all participants actually contributed CFS samples, and we had 75% of the total CSF samples that were supposed to be collected. So, we have a very robust amount of data. We've actually done some analyses. First, because it was due to the pandemic and the hospitals closing, I can have statisticians comment on the fact that it's a very fair assumption to assume it's missing at random. And we looked at multiple imputation and actually generating imputations based on the observed values over time and we're able to show that if we look at the data that was observed data compared to those that are multiple imputed, it actually does not change the conclusions. And I do look forward to talking about correlations of the biomarkers as well.

Dr. Ahsan: Okay, if we could go to Dr. London.

Dr. London: Thank you. Yes, I have two short statistics questions. What if the week 28 assessment was missing for the ALSFRS score? That endpoint is needed to determine a patient as a responder. Did you do last observation carried forward?

Dr. Lindbergh: So, on the primary endpoint if a visit was missing, we computed the slope across all visits based on the observed data on the average change from baseline we used an MMRM model and we look at the longitudinal trajectories and then of course we're estimating the average change. What we furthermore did, especially based on if there was data missing at week 28, these were pre-specified sensitivity analyses. So, we looked at multiple amputation missing at random, missing not at random, and then we also explored using a joint longitudinal model. Estimating the survival that was observed in the trial and using treatment-level survival that would appropriately impact the efficacy conclusions. And all of those we submitted this as a briefing document to the FDA early after we unblinded show that the robustness of the clinical data that we're speaking to the efficacy the treatment effects actually were held across all of those analyses.

Dr. London: And you talk about database lock, and you didn't look at any of your you made your pre-specified selection of biomarkers and certain analyses before database lock. But that's different than having performed interim analysis. This database lock, is that the same as the timepoint at which you would have begun analyses after database lock?

Dr. Lindbergh: So, we submitted a second statistical analysis plan on the biomarker data where we identified all the biomarkers and the methods that we would use to analyze the data that was before any analyses were done and before the unblinding of the trial. That's correct.

Dr. London: Thank you.

Dr. Ahsan: Okay. I'm actually going to put it back to the order in which we had it when they were originally asked. So, Dr. Wu, if you'd like to turn on your camera and unmute yourself.

Dr. Wu: Yeah so, I have a question about the MSC product. I think, as you know a lot of companies use different types of MSCs for cardiac, for bone for muscle and so forth. In your

product, you're adding something to release the neurotropic factor, but it's not clear to me what it is. Probably because it's proprietary. One question I have is this something that you add to the cells to cause the cells to pump out more neurotrophic factor. I assume when you inject it into the CSF space, how long does that cell keep on pumping out this neurotrophic factor? Because in vitro, once they're exposed to the factor, it pumps it up. But in vivo, once they're no longer exposed to the exogenous factor, a lot of times they'll stop by pumping it out. Have you guys done that type of kinetic study to see how long? Because if it stops within a couple days, then it's just back to the regular mesenchymal stem cell product that has a lot of variability based on the comorbidity of the patients, right?

Dr. Lindbergh: Okay, great questions. I'll take the first stab at answering and then I'll ask Dr. Levy to join me. So, I'd like to show a set of neurotrophic factors. That are exhibiting the changes in four different neurotrophic factors. And so, these are within the same individuals. So, the light blue bar and the dark blue bar, by each number below it, are the same people. And so, first is based on the naive mesenchymal stem cell from that individual, the secretion level of neurotrophic factors, and then the dark blue bar is then the corresponding mesenchymal, the neuron or mesenchymal neurotrophic factor secreting mesenchymal stem cell level of each of these neurotrophic factors. And so, you can see that for all these individuals you have a marked increase in the secretion levels of neurotrophic factors.

The second point I'd like to provide is that our brain record data from Phase III allows us to see of the nine neurotrophic factors that we studied, eight of them had significant increases in the trial, a significant treatment effect relative to placebo. And we can see, I'll show you this slide, some of them, for example, VEGF increased 365% at week two. And as was pointed out in the discussion during the FDA Q and A, this is the only time we measured a two-week interval.

And it was really out of consideration and the burden of trial participants we were already taking seven CSF samples. So, we wanted to have one measurement at two weeks. We don't have that as was noted. It's a very astute observation between eight and 12, so we don't know if it continues to go up or after 16 and 20. But what we can see is that the neuron-treated levels remain elevated. I think it says 15% at week 20. So, we do know the cells at a treatment level, and you can see actually the variability bars are quite small. These are confidence intervals, 95% confidence intervals. So, we can see that placebo across 20 weeks remained quite unchanged and flat and the neuron arm I can actually see on the bigger screen was 156% increased from baseline at the end of the trial. So, we do know that these levels are remaining high and this is what's very important, to come up with these calculations we're looking at each individual's baseline and then their subsequent levels. And so, we're showing how that average is changing but relative to each individual's baseline, which is very important given—

Committee Discussion

Dr. Ahsan: Great, thank you, Dr. Lindbergh. So, we are very much pressed for time, and it is critical that the committee have the opportunity to discuss the various points among themselves and then move forward. So, Drs. Fishbeck and Li, I know you have your hands raised. If we could just start our internal discussion among the committee, and then if you have those questions still, we can then bring back the sponsor or the FDA to answer them appropriately. But we do need to start our discussion if that works for you. So, along those lines, I think we're at the point, yes, Marie, to read the questions for discussion. Okay I'll go ahead and read them.

Ms. DeGregorio: Yes, that's correct.

Dr. Ahsan: So, the questions for the committee today is one, please discuss the data presented in support of effectiveness for treatment of mild to moderate ALS, including consideration of the

mechanisms of action proposed by the sponsor, biomarker data, including neurofilament data, and the clinical data.

Number two is a voting question. For that, the question is, do the data presented demonstrate substantial evidence of effectiveness for treatment of mild to moderate ALS? And the responses will be yes, no, or abstain. If in the voting question, the majority to the answer is no, we will then please discuss potential designs for a trial to demonstrate substantial evidence of effectiveness for MSC-NTF for the treatment of mild to moderate ALS. So, those are the questions.

Now, I do want to emphasize that this discussion time is for the committee members to discuss among ourselves. If we do have a pressing question that needs to go out to the sponsor or to the FDA to help inform our discussion. We can do so. I think we can move to question one, is that the next slide? Okay, so now we're going to start with discussion of question one. Please discuss the data presented in support of effectiveness for treatment of mild to moderate ALS, including consideration of the mechanisms of action proposed by the sponsor, biomarker data, including neurofilament data and the clinical data. To let everyone on the committee know, we have parsed this question out into four parts, and we have a lead discussant that has been identified and agreed to start the conversation on the MOA, the neurofilament data, the biomarker data, and the clinical data. And so, for that, I will ask Dr. Fischbeck to discuss the topic of proposed mechanisms of action. Dr. Fischbeck.

Dr. Fischbeck: Yes. Thank you. Marie just asked me that yesterday, or last night, to take this on. I think I don't have a lot to say, except that and I would invite questions or comments from other members of the panel on this topic, but just with regards to the mechanisms of action, so I should note from a historical perspective that neurotrophic factors for ALS and other neurodegenerative

disease have a long history that goes back in terms of at least an idea over 50 years. I remember it early in my training with nerve growth factor. And in ALS specifically, there's been a number of individual growth factors, neurotrophic factors, rather, that have been in clinical trials over the years. And with a lot of public interest, a lot of patient support as well as investigators and similar stories with what we've been hearing today. But unfortunately, none of them worked despite high hopes that they might, based on preclinical studies. So, I'm interested in what others have to say, in my mind the approach of using multiple neurogenerating, multiple neurotrophic factors from cells that are transplanted into the patients is an interesting and relatively novel idea. Maybe each one alone may not have a benefit, but a collection of them, maybe up to five or six produced by these cells could have an effect where the single factors do not. And the further question related to that is did the sponsor adequately assess the mechanism of action to see whether these cells are effective in preclinical and the clinical studies? And that support this overall approach through the cellular studies, animal studies, and then the clinical studies. And there are, as we've been hearing over the course of the day, a number of drawbacks to the studies have been done, or at least the results that were obtained and be interested in what others have to say about that. If it has not been adequately addressed by the company so far, what else can be done to improve it, to better test this hypothesis of multi-factor treatment for ALS with neurotrophic factors? So, I don't know.

Dr. Ahsan: Great.

Dr. Fischbeck: Just open it up to anybody else who wants to comment on that particular aspect of the question we're asked.

Dr. Ahsan: Perfect. Thank you. And if folks can raise their hands. In terms of the clinical trial design that might help better identify MOA, that conversation will happen at the end. That is question number three. Dr. Rajiv Ratan.

Dr. Ratan: Yeah, I have to say that I'm a little perplexed by the lack of preclinical data that was presented to us. And I think this was highlighted by some of Mark's questions about growth factors that theoretically would work in the spinal cord, actually getting to the right place. But most of all, I think many of the studies with stem cells start with a robust phenomenon or phenotype in terms of behavior, and then you go back to try to figure out what might be mechanisms that you could actually use as a guide in vivo to help you be assured of target engagement, but it seems like none of the things have been done to try to convince us that the concentrations of the growth factors that they have could be adequate. That they're reproducibly produced. That they're produced at a consistent level that might have a behavioral effect, and the fact that many of their primary and secondary outcomes are negative, maybe amplifies why moving forward, it's really important to have these mechanisms of action and quality control mechanisms in place.

Dr. Ahsan: Great, thank you. Yeah, I'd like to build on that, which is they themselves proposed that the MSCs have a function and the NTFs, but I didn't see any presentation of data related to the MSCs and their role and what they're expecting those to do specifically separate from the NTF as an NTF secretion vehicle. Thank you very much. Dr. Gold.

Dr. Gold: Yeah, look, I come from a small molecule background where dose and target engagement are the critical thing. So, there was one slide that the sponsor showed where they showed the variety of different trophic factors on an individual patient basis. And what struck me there is that it seems like it's almost individualized data. Although they seem to induce a variety

of trophic factor expression, it didn't seem to be a consistent pattern across subjects. So, what I left struggling with is the variability in the data related to this kind of unique profile for each subject, and I don't mind at the end of one experiment, but maybe we need to think about if you can't really tell the cells I need you to produce X amount of factor 1, 2, 3, whatever it is. Then I'm wondering whether the issue is that this really becomes a distributional problem. In fact, you're not providing a kind of a dose, although giving a certain number of cells, but you're not giving a particular dose. You're actually giving a range of doses of these various trophic factors. And I'm not sure that either the sponsor of the FDA. Have looked at the data taking that kind of variability of the trophic factor expression into account. So, I'm struggling with what the patients actually get exposed to.

Dr. Ahsan: So, let me just push on that a little bit. So, you're, in terms of the variability, you mean both in terms of the increases in which neurotrophic factors as well as a combined pattern of the cocktail?

Dr. Gold: So, if you think about it, and I don't know, I don't have access to that slide, but the sponsor just showed that slide where they are.

Dr. Ahsan: Right.

Dr. Gold: And what the answer was? Yeah, we induce expression of all these terrific factors across. But the ratios are not the same. Right?

Dr. Ahsan: Right.

Dr. Gold: And they're not the same for every patient. And I don't know that they're the same over time. And so, if you have that, it's essentially the equivalent of an exposure response model. We never did any sort of PKPD, because there's no PK here. But if you know that you're giving people a different set of trophic factors, and you don't know whether a subject is going to

respond better to traffic factor A, or B, or A plus B, but not C plus D, it just seems that we have this quasi-random selection of trophic factors that people are exposed to. In the back of my head, I'm thinking there may be a way to actually look at what patients were actually exposed to and say, hey, when you had a particular ratio, a particular pattern, did that reflect itself in an improvement?

Dr. Ahsan: Yeah, exactly. There was no model to indicate the elevation ratios that they expect.

Dr. Gold: Correct. Correct. Exactly.

Dr. Ahsan: Or a rated equation. Yes.

Dr. Gold: Exactly. So, I don't know if there's any considering, but in my mind, that would be a very helpful model to understand—

Dr. Ahsan: Yeah, perfect.

Dr. Gold: —whether what subjects were supposed to actually drove what the response was.

Dr. Ahsan: Yes. Great. So, Dr. Tuszynski, please.

Dr. Tuszynski: Yeah, thank you. So, in hearing the presentation, it seems to me that in this program, a trophic mechanism is more of a hypothesis than a proven bit of data. Generally, in the large preclinical literature that has transplanted marrow stromal cells for a variety of disorders, not just ALS, but spinal cord injury and others, stroke, for example, people bring up the hypothetical possibility of growth factor secretion and some studies have shown growth factor secretion by these cells in vitro prior to implantation. We haven't been shown that data with these particular cells in great detail, but we did see that one slide. And in that one slide let me just say, I've spent the last 30 years trying to bring growth factors to human clinical trials to test the

hypothesis that they could ultimately be beneficial in the treatment of human diseases. And there are a potent group of molecules.

And in previous clinical trials that have infused the growth factors themselves, the recombinant proteins directly into the CSF, and Jesse Cedarbaum, who's on this call, did one of those first trials when he was at Regeneron with CNTF. It was basically found that even high concentrations of growth factors infused into the CSF did not reach the neural parenchyma very well at all. That was the case with nerve growth factor infused intracerebral ventricularly with GDNF intracerebral ventricular infusions and others. When infused into the CSF, they don't penetrate the parenchyma very well and that's why the field shifted about 20 years ago to direct intraparenchymal infusions or gene therapy as I'm doing it now. And these are with high concentrations. So, when we look at the change in growth factor concentration that we saw briefly in the one slide presented by brainstorm, it looked like the elevations and growth factors were approximately 50% above the endogenous levels created by the cells. And that's a small change to expect that small change to be translated into parenchymal penetration in my opinion. Just wanted to say that.

Dr. Ahsan: Great. Thank you. I think this idea of delivery and bio distribution and what concentrations are needed in order to create that gradient is an important question. Dr. Li.

Dr. Li: Thank you. I just want to bring all the panel members to a 5,000 feet high view on this issue that when you look at the data that Dr. Snyder presented when the stem cell goes into the nervous system. And he illustrates the many things that cell is doing, including the cell migration integrations and neutralize toxicity from clear sales, et cetera, et cetera, there's a long list of those. But if you look at the big picture of ALS, there are so many mechanisms that have been described including the dystrophic neurotrophic deficiency, mitochondrial problems, axon

transport, all these. So, the question I have is, if you look at this big picture, why do we use the MSC and then we focus zooming into this neurotrophic factor, but not everything else? What is the primary reason and rationale that led us to believe that this neurotropic factor is the predominant effect of affecting the ALS outcome? Why can it not be something else? So, that's something that I don't understand very well from the presentation that I hear so far.

Dr. Ahsan: Right. I agree. So, they're also putting in NMCs that do a whole host of things and what is their role in the mechanism of action or the observations that are noted. Let's see. Dr. Wu.

Dr. Wu: Yeah. So, I want to get back to this question about the growth factor and how long they're being secreted. Because I think, for example, the product is just MSC. So, the patient, then nobody gets excited because it's been used for a lot of stuff in many of the trials that don't work. Now the product is some type of exogenous cytokine stimulation or something to stimulate the growth factor being released. I think the company showed us that, oh yes, it's higher. But I would assume that's 24 hours after exposure. But what happens to that level in vitro at 48, 70 to 96 hours? I would assume it comes down. So, to show us the data, the in vitro data of how much the growth factor persists after stimulation, that'll be helpful. I think the in vivo data, that was a cells versus placebo, right? And so, I don't know if those growth factors being released is just from the cells itself or because, I don't think if I remember correctly, your placebo is not cells, right? It's not MSC without stimulation. And so, in that case, I don't know if those growth factors that you're showing is just from the cells versus the cells stimulated to release the neurotrophic growth back. So, the key here is giving us more information about the kinetics of the release and how much, how long that's the key to me. Yeah.

Dr. Ahsan: Great. Thank you. Kathleen O’Sullivan-Fortin.

Ms. O'Sullivan-Fortin: Hello. I cannot shed much light on some of the more scientific facts that people are debating, but I do want to bring up the fact that this question addresses the data presented. And I just want to remind people to go to the entire docket which includes more than 1600 public comments that have been registered. I don't want to assume anything but I'm going to guess that I am one of the few that even attempted to slog through hundreds and hundreds and thousands of comments. And what do we do with the testimony shared today? It was not necessarily by the sponsor and certainly not by the FDA. But what do we do with the patients and the ALS families and the ALS organizations and other doctors that are not present on this call and on this meeting that have taken their time to send us, yes, albeit anecdotal evidence or when it's an end of one it's anecdotal. I just don't want people to lose the forest for the trees. I don't want you to miss the point that these are not just cold data points. One point matters to these patients and I have read through, and thank you to the people out there who took time to submit this evidence This is evidence and if we can if we don't have the ability to really draw it together and make sense of it, does that mean that there is no help for this community or that this just isn't something that the committee has to decide. But I do want to just draw attention, no matter how tight we are on time, to the fact that there are thousands of people who wrote in and are waiting for this answer and who shared their experiences, being part of the trial with the positive impacts that they experienced in their own lives.

Dr. Ahsan: Thank you very much for that perspective. That is very helpful. And it, of course, should always stay top of mind. The patient population that will be affected. Thank you. Dr. Lynn Raymond.

Dr. Raymond: So, I share a lot of the same comments and questions that have already come up. I just wanted to add that in most clinical trials, we do single therapeutic testing because it becomes

way too complex to figure out which one is working. If we use more than one at a time. And here, the hypothesis is that it's a group of neurotrophic factors is not really clear. First, if there's enough of them to actually make a difference in the volume of CSF or how long they last, but just to start, it's a bunch of them. And we're not really sure if there's one or two that are really the ones that are beneficial. If there are any beneficial ones that are, again, sticking around long enough.

As far as the stem cell being used, I guess it's just a vehicle to try to avoid using a genetic method and because it's from the patient, you use it from the bone marrow. But somebody asked the question about engineering stem cells that are, uniform off the shelf. Everyone gets the same thing and at least it's a neural stem cell that is expected to integrate because that was a big point of Dr. Snyder's presentation that you need to think about what your goal is, what tissue do you want to treat. And so, you need a stem cell that's actually going to fit that niche. So, I'm just bringing those up as things to think about for mechanism of action. But not necessarily to tell them they need to do something else for the trial with a different type of stem cell. Just as a point to consider.

Dr. Ahsan: Great. Thank you so much, Dr. Raymond. Dr. Gold.

Dr. Gold: Yeah, so I'm going to put my industry representative hat for a moment here and address the issue of what about the patients and their families? Because I also participated in it to first-in-outcome. And that was a very interesting discussion as well.

Look, the first comment is that I don't think any of us go into industry or many of us going to industry because we're equally frustrated with the lack of treatments and the dismal outcome for many of the patients we took care of. So, I want to make sure that anybody and everybody listening to this conversation understands that this is not a sterile discussion that those

of us on the industry side are as motivated or as passionate about finding something to help patients with ALS, other diseases, as the families that are involved. We're not living it. Some of us are actually living it too. So, I have a colleague that I work with another company who actually died of ALS while he was still working for the company. So, it hits close to home. The reason I'm making the commentary is I think we need to be very guarded about the weight that we put on anecdotal data. And I'm sorry, I'm going to give an example and I hope it doesn't come across as trivial, but nobody provides testimonials for diet, supplement for diet, for weight loss products, when they gain weight. Right? And so, my heart goes out to the people living with it, folks who think they've seen benefits. But I think that the issue here is we have to be objective and we have to be data driven. We don't have things that are curated, but I can tell you that finding patients to go into ALS clinical trials is getting tougher. Controlling for the multiple drugs that are approved is getting tougher. And it would be a very different discussion if the drugs that are being approved were radically effective, in which case, there's no question that these would become rapid standard of care. But I just want to put my hand up and say, look, I treated patients' ALS, there are folks that I know that are affected. It is an incredibly devastating disease. No question about it. But I really want to caution around being, swayed by anecdotal data. Multiple anecdotes are not the same thing as data and this is from somebody who's been in this industry for almost 30 years now.

Dr. Ahsan: Great. Thank you. Actually, I am going to go to Dr. Lisa Lee to make a comment. I think it is likely very relevant at this point.

Dr. Lee: Thank you so much. And actually, I really do want to comment on the heels of Dr. Gold's comment. And I would just like to say that there's absolutely no doubt that ALS is a devastating disease and that there's an urgent need for treatments that are effective. I think we

heard from our public commenters, patients and families need hope. But providing false hope can be ethically problematic and false hope is provided when the probability of a positive outcome is overestimated. And I think that seems to be the case here creating false hope can be considered a moral injury and the use of statistical magic or manipulation to provide false hope, I think, is problematic both in this current application as well as for the integrity of the drug and device approval process for at large, so I'm worried about what was demonstrated today that might be false hope for persons with ALS for their caretakers and of course, for their loved ones. Several comments that generate false hope that gave me pause today are things like efficacy was shown in four clinical trials, and I don't think the data consistently support this claim or something like the totality of the evidence. It shows efficacy and I think post hoc and biomarker analyses here adding that to the totality of the evidence is mixing evidence with anecdote. And this generates positive outcomes that I believe are overestimated. I think there's no denying that the effective treatments are needed, but comments such as 30,000 people with ALS will die while we wait for another trial, these kinds of comments are misleading. Approval of this treatment today, even if it helps every person in the same way it helped the commenters will not prevent deaths from ALS for these 30,000 people. And I think this kind of rhetoric fuels the false hope.

Now, on the contrary, ethically in situations where disease is severe and treatment is not harmful, in ethics, we talk about a variation on the precautionary principle, which would support making this treatment available. But I think as Dr. Snyder said early in our conversation today, even if therapy is safe, there can be other harms, psychological harms, he said. And I would add to that financial harms, desperate families spending everything, mortgaging their futures on a treatment that could very well be built on a foundation of false hope.

So, I hope as we move forward, we remember that is always the case in ethical gray areas, tensions between values, in this case, the value of hope against the value of harm that these are inevitable and definitive answers are often elusive. There is often more than one ethical way forward each with its own set of risks and benefits. And in this case, I think one reasonable approach, given the conflicting evidence that's been presented the conflicting values related to hope and harm and the lived experience of the affected persons we heard from today is to request this applicant to do further work to show efficacy, which would provide true hope for these patients and their families.

Dr. Ahsan: Great. Thank you, Dr. Lee. I know it wasn't directed to question one, but the last few comments of are important to give us a balance on perspective. As we move forward, I do know that the sponsor wants to make a couple more comments, but at this point, I would like to do it after we have the neurofilament data discussion. Dr. Fischbeck potentially, you can wrap your comment up into the next series of conversations, which are not unrelated, so it'll still be relevant, I believe. So, Dr. Ronald Liem, if you could start us off on the discussion related to neurofilament data and how it contributes to our understanding of product effectiveness. And I ask everyone that speaks moving forward that we try to be direct and to the point, just because we do need to make sure that we have a full, robust discussion on all the topics that we have on hand. So, Dr. Liem.

Dr. Liem: Okay. So, I looked at the neurofilament data and I think the FDA presented a very good explanation of the data and why it isn't quite what the sponsor is suggesting. The sponsor is suggesting that the neurofilament's levels in the CSF go down by about nine or ten percent as a result of the treatment, but, again, the FDA really looked at that data a little bit more carefully and was not convinced by that data again. I think the FDA also mentioned the data with the

Tofersen drug, which I looked at those papers and there was a big decrease after treatment with Tofersen after 12 weeks it went down 50 to 60% and then I think ultimately was down 67%. And the FDA then approved actually neurofilament as a biomarker for the ALS endpoint. So, the data that they presented was not as convincing, was not very convincing at all. And furthermore, the reason I asked the question was, I was wondering if perhaps if they just looked at the data from the mild to moderate ALS cases whether they could, get better data. Fact that they didn't present it made me think that it probably didn't. And I think the answer was that they did. And they said was really very similar. And the relationship between neurofilaments and the efficacy with looking at the ALSFRS-R data that was completely not convincing and I think it was the most random plot that I've ever seen that, through which a line was drawn. Anyway, that's how I feel. With regard, again, to Tofersen, they actually found that the neurofilament result dropped already before they saw an improvement. And so, they actually were able to use that as a marker for efficacy. And as I said, that was not just, a five to ten percent decrease, but it was more like a 50 to 70% decrease.

Dr. Ahsan: Great. Thank you, Dr. Liem. Does that mean that your thought is that the neurofilament acts more as a correlative rather than a causative marker?

Dr. Liem: It's definitely not, it's a correlative. So basically, neurofilaments are the major cytoskeletal element in myelinated axons. So, the fact that the myelinated axons are degenerating on the neurofilaments then get secreted into the CSF. One thing that may not be clear is you may wonder why neurofilaments just don't continuously go up, they do get degraded. So, the fact that they stay constant in the non-treated cells and even in the placebos is a fact that degeneration continues. And so, that's all essentially new degeneration. And in fact, then if it drops, that means that degeneration has stopped or is slowed down.

Dr. Ahsan: Got you. Yeah. I did not mean to be causative, trying to multitask here, but in fact trying to understand how it relates. Thank you very much for that clarification. Dr. Tuszynski.

Dr. Tuszynski: Dr. Liem might have mentioned this, but I just wanted to point out too that. There was not an expected correlation between the neurofilament light levels and cognitive and performance on the ALS functional rating scale. There was an inverse relationship, which undermines the validity of the data to some extent. It was an unexpected relationship and that relationship went as expected in the antisense oligonucleotide trial.

Dr. Liem: Yeah.

Dr. Tuszynski: That's another problem here.

Dr. Liem: There was a very small change, but whatever change that was wasn't the wrong way. You're right. Should have mentioned that. Sorry.

Dr. Ahsan: What does that mean for us here? Because if in a separate study, what we're seeing is that correlation, does it say something about the grading scale, or does it say something different about mechanism of action?

Dr. Liem: I don't really think it addresses mechanisms of action. I think basically it says that the degeneration continues. And so, the fact that there is no correlation just means that nothing happens. Maybe it does address mechanism of action in a sense that there isn't one. That there is no improvement. And the neurons do not stop degenerating.

Dr. Ahsan: Alright. Thank you. Dr. Ratan.

Dr. Ratan: Yeah, I think one other possibility that, again, it would be simply a control, but it does seem important for the company to do an experiment where they show in vitro that whatever is secreted by the cells doesn't independently degrade or elevate neurofilament independent of what happens to the tissue. So, that may be a reason that there might be

confounds, but I also think that, and maybe this is going to be addressed, I think Ron asked if you look at the subgroup that actually improved, was there a greater change in neurofilament in that group? And it didn't sound like there was. So, those are just two comments.

Dr. Ahsan: Okay, I do think we had a little bit of a pointed question that we can allow the sponsor to answer, but I encourage the sponsor to keep it very brief and get direct to the answer. So, Dr. Lindbergh, did you want to address that element of the neurofilament?

Dr. Lindbergh: Yes, I do. So, we had an analysis that was in our briefing document that shows, which is coming up, that shows the relationship between change in neurofilament light to change in the ALSFRS-R. And this actually was the exact analysis that was done in the Tofersen submission in a really critical part. Okay, so you're going to see we know ALS is a very heterogeneous disease. We've heard this discussed in multiple times today. This analysis was central to the Adcom with Tofersen accounting for variability in ALS in neurofilament light. And presenting the neuron-driven changes in neurofilament light and comparing that to what's the relationship to the neuron-driven effects in the ALSFRS-R. And we find that there is a correlation. It's going in the direction that one would expect. Individuals that lose more neurofilament light, we see less functional loss. And this is a really central point. I'll stop after I make this point, let you get back to your discussion. But in all of our analyses, it is really critical that we take into account the heterogeneity of the disease versus look at simple relationships and not think about the fact that we're modulating multiple biological pathways in parallel.

Dr. Tuszynski: Why are these 48 patients in the analysis?

Dr. Lindbergh: So, this was at the week 20 and we started with those that had observed data, and then we also did it under multiple imputation because of the pandemic, CSF values that were

lower at this visit. And we saw consistent relationship and negative relationship but relying on early all the observed data that was earlier in the trial to use multiple imputation models.

Dr. Ahsan: So, just to be clear, this is a population of patients that for which you actually had biomarker data as well as—

Dr. Lindbergh: ALS for the first time.

Dr. Ahsan: But was it for only the patients that were the stratified population or was it the entire population?

Dr. Lindbergh: This is for the individuals that didn't have any zeros at baseline. So that we're able to look cleanly at the ALS functional rating scale. When we come back, I'd love to show another slide that contrasts those with the floor effect versus those without the floor effect and also factoring in heterogeneity.

Dr. Ahsan: At this point, we'll have to put a pause on that. Dr. Liem.

Dr. Liem: Yeah, I'm just commenting on that particular figure, which I think is figure 41 that they presented. If you didn't put that line in there, really. I think it would look really quite completely random. And the line shows a bit of a slope, but I think there are a couple more points in the data that they showed in the document that even make it worse. So, I'm not sure that particular figure is convincing.

Dr. Ahsan: Okay. So, I think Dr. Witten has a comment.

Dr. Witten: Thank you. I just want to say this is supposed to be the AC's discussion, but since the sponsor commented on this question, I think that there may be someone from FDA who would like to respond. Also, I don't really want to make this a back and forth, but I would like to put back up slide 40 from FDA and Xiaofei, are you going to comment on it or who shall I call on for that?

Dr. Wang: Thank you very much, Celia. I would like to defer to our pharmacometric consult reviewer, Dr. Vishnu Sharma, who also has been involved in the review of Tofersen to comment on for this topic. Thank you.

Dr. Witten: Can we have backup slide 40? And then after that we'll leave it to back to an AC.

Dr. Ahsan: Thank you. Thank you, Dr. Witten.

Dr. Sharma: Hello, this is Dr. Vishnu Sharma, pharmacologic reviewer. I have also done the analysis for the Tofersen case as well. And I would like to highlight that there are multiple limitations of the applicant's current causal inference analysis, which makes us different from the previous Tofersen submission. The first one is the intent of the analysis. So, in the Tofersen case, the intent was to adjust for imbalances in baseline variables, especially plasma NfL. So, in their case, there was 31% imbalance in NfL in the mITT population. However, in the current case, there is no imbalance in the NfL value. So, there is a limited utility of this analysis. Now, second thing is a selection of the population. So, in the Tofersen analysis, the analysis was done on ITT population with no data excluded and the result or the trend that one can see from their model was the same as what observed data was showing, it was just more refined.

Now, in the current case, almost 50% data has been excluded on the pretext of floor effect. We have already heard the discussion of the floor here. So, due to this exclusion, a lot of subjects who have shown higher disease progression has been excluded. And therefore, the data or the model predicted trend are not in line with the observed data. And lastly, I would like to also highlight that there are also various clinical covariates that we have considered for the Tofersen case, which in this case are not considered, one notably includes SVC. So, there are differences besides some other technical differences. That's all from my side.

Dr. Ahsan: Great. Thank you very much. In order to keep things moving so that all thoughts can be presented, Dr. Tuszynski, would you like to present on the topic of biomarker data and how it contributes to our understanding of product effectiveness?

Dr. Tuszynski: Okay, and by biomarker, I take it you mean the neurotrophic factors, yeah?

Dr. Ahsan: Yes.

Dr. Tuszynski: Okay.

Dr. Ahsan: Yes, thank you.

Dr. Tuszynski: So, the neurotrophic factors that were the subject of emphasis were BDNF, VEGF, hepatocyte growth factor, and LIF, Leukemia Inhibitory Factor. And in the literature, there is evidence to support an effect of BDNF and LIF on motor neuron survival, and there's also evidence to support their effects on upper motor neuron survival in the motor cortex. I'm not familiar with evidence that suggests that VEGF itself directly affects motor neuron survival in the spinal cord or the brain, but there might be a study I'm not familiar with. Then, with regard to hepatocyte growth factor, it's considered a trophic factor for several spinal cord populations though. Again, I'm not exactly aware whether it's been shown to have a specific effect on motor neurons. So, of these, the data from the Phase III clinical trial really showed no difference that was substantive or sustained in any of these. In the case of vascular endothelial growth factor, there was this rise that was shown at two weeks after injection and as was pointed out, we didn't have another two weeks sampling after the subsequent injection. So, we don't know if there might have been a boost. All we know is that there was this boost in VEGF, and it would have been informative to hear more from the sponsor why they think this boost in VEGF might have been useful for motor neuron degeneration. Did they think it was going to induce vascularization,

or did they think it was a direct trophic factor induced effect on the cells? And if the latter, again, I'm not familiar with such literature, but maybe it exists.

The amount of the various growth factors that was sampled in the spinal fluid, other than VEGF at the two-week time point, however, represented very little departure from the placebo data. And the point that I was making with regard to mechanism of action about half an hour ago was that in growth-factor trials, if one doesn't attain very substantial boosts and growth factor levels, even with substantial boosts in growth factor levels in the spinal fluid, there's very little evidence that those growth factors penetrate the spinal cord parenchyma. So, with the kind of very modest changes, if any, that we're seeing here, I'm not convinced that there's evidence that these biomarkers could be penetrating the parenchyma of the spinal cord to provide a beneficial effect. I haven't seen data that is compelling to indicate that these could be biologically meaningful elevations that are represented in the tissue itself. And I did explore that question with the sponsor in the question period initially, and I believe the answer was the growth factor levels were not measured there because it's difficult to do so. And it can be done, and I don't think that the data exist. Those are my comments.

Dr. Ahsan: Thank you very much. That's very helpful. I think in general, some questions about the selection of the subset of markers, the levels at which they're expressed, all of that is quite important. Are there any comments from the committee, particularly on this aspect of the biomarkers? We've had quite a bit of conversation on the biomarkers throughout. Are there any more additional comments that need to be made at this point? Great, thank you, Dr. Tuszynski. So now, if we could move to Dr. Alexander to start us off on the discussion on the topic of clinical data in support of effectiveness.

Dr. Alexander: Yeah, sure. Great discussion by the way. Thus far, I think the clinical data are helpful. They're just disappointing. And frankly, they're hard to reconcile with the compelling anecdotal evidence of effectiveness that we heard from the public speakers. We have a single trial at the dose and formulation that's proposed. Although the Phase II study didn't suggest efficacy. And frankly, both safety and efficacy in the Phase II study are hard to interpret because it was a different dose schedule and route of delivery. I did ask why they gave people 19 muscular injections or something if this doesn't cross the blood-brain barrier, but I didn't really understand the response. But that's a little bit neither here nor there.

Unfortunately, we have a single study, the Phase III study at the dose and formulation that's been proposed, and it unfortunately didn't achieve evidence of efficacy for either the primary or the secondary endpoints. I think we heard, and I certainly agree as an epidemiologist with the FDA's assertion, that post hoc analyses are subject to strong and untestable assumptions. And guidance may allow for the approval of a product based on a single pivotal trial plus confirmatory evidence, but not no clinical trial plus confirmatory evidence. Not a trial that's not successful in demonstration of efficacy. And frankly, although there are some, I think, unfortunate examples, I would argue, I think if you look at the majority of cases where FDA has used a single trial it's been with very strong evidence to support the approvals. The floor effect is possible with any bounded rating scale. I thought it was interesting to hear that, but then also I did appreciate hearing from one of the sponsor’s speakers that's addressed one question which I had, which is if it's present with any bounded scale, wouldn't why would It wasn't this anticipated, before the trial was done? But I think this addressed that a bit and spoke to the fact that it wasn't, it generally hasn't been seen. The effect hasn't been seen as strongly in ALS scales previously, and so on. Maybe it wasn't expected that people would be with a severe disease as

they were, but with all of that said, the analyses of the floor effect, I didn't find terribly convincing. And frankly, I think the FDA's analyses of that demonstrate why post hoc analyses, while they can be helpful and supportive, aren't sufficient in weight to overturn a negative top line result. And I guess the final two comments that I'll say one is that the rap or progressor or language is nearly identical to other committees I've served on, including Aducanumab in the case of Alzheimer's disease and at a person in the case of Duchenne's. And this sort of language is, I think, an understandable way to try to understand and make sense of disappointing topline results, but there will always be rapid progressors, right? There will always be people that respond more and less to a treatment. And of course, if you remove those who respond less, you end up with those who respond more.

So, I'm very interested in the sponsor's response to the same question I asked the FDA, which is, if you were to design a new trial, how would you do it differently? But it sounds like we'll have a chance to advise the sponsor on that shortly. And so, I'll conclude my comments with that. Thank you.

Dr. Ahsan: Thank you very much. And exactly right. We are meant to give some guidance on that, aspect. Dr. London.

Dr. London: Yes, just to follow-up on the floor effect. I think that if you believe there's a floor effect that actually is evidence to me that, unfortunately, this is not an appropriate endpoint to try and measure benefit of the treatment effect. So, if you believe the floor effect, I think it just leads us to the fact that we need to do better on a better primary endpoint. And unfortunately, I understand that this has been a standardized instrument used in ALS for many years, and we're not going to come up with a new instrument overnight. But hopefully there is something better and we can talk about that in the clinical trials proposal time slot.

Dr. Ahsan: Thank you, Dr. London. Dr. Johnson.

Dr. Johnson: Yes, thank you. I think I also agree that I found the clinical data not compelling enough to support efficacy and I wanted to particularly call out the imbalance in mortality, which has been brought up a couple of times and for me at least raises some safety concerns. I know people talked about the other potential side effects, but that type of imbalance would need to be addressed in future trial designs as it says beyond the primary endpoints that there may be a mortality issue.

Dr. Ahsan: Thank you, Dr. Wolfe.

Dr. Wolfe: Yeah, I'll just add on to what Dr. Johnson just said. We've talked about the survival data. When I was looking at the data, the actively treated arm, this was in the largest collection of adverse events, life-threatening adverse events. Bulbar and respiratory adverse events were higher in the actively treated arm. Again, I will bring up the point that the randomization, the burden of bulbar disease actually seemed to be less in the actively treated arms. So, there's something there that is not jelling. And when you add that on to the survival data it creates concern, at least for me.

Dr. Ahsan: Thank you. So, anyone else who would make like to make a comment? Not only on the clinical data, but the biomarker data, the mechanism of action, anything related to question one. Great, I think we had a good, robust, dynamic conversation. Let me try to pull it together a little bit and apologies if it's not so well-organized, and then if I miss something. Of course, potentially committee members can add on to what I say. So, I think, in general, the thought is the mechanism of action is not clear. And the sponsor did not necessarily put forth a clear hypothesis related to the mechanism of action in terms of the MSC roles and the NTFs.

It is understandable that at this point, it's early so that the hypothesis related to the trophic mechanism might be unclear, but there was still a lack of preclinical data that was presented. And in general, there was a lack of data that was presented that was unfortunate and makes it such that the committee has to make decisions based on what was presented. There was also some discussion that there are multiple NTFs and the thought was that they together have a function. However, the dosing of those and the target engagement of that was not clearly proposed forth in terms of the levels of elevation, potentially a weighted equation of the different ones that would help create a pattern that we saw in each individual patient cell types as they got overexpressed in this product of the MSC-NTF. It was also unclear how it would get delivered into what tissues. The thought is that's unclear, even when you have high concentrations, but with the low concentrations of some of the markers that were selected, that becomes further confounding as to how you would expect what tissues they would be in and how long that they would persist. The lack of data of showing even their persistence and expression in vitro makes it even more challenging to interpret how the in vivo environment might modulate that. So, in thinking about the biomarkers further, what governed the selection of those markers? How were they justified? How we expected those to function in those low levels, we usually expect a substantial boost in the trophic factors that we're hoping to have some role and mechanism of action. And it wasn't clear that was anything that was happening with this product. Again, we have no way to track the concentrations that were happening in vivo, nor how long they persisted but there was a lack of preclinical data that was presented to even give us some sense of that.

In terms of the neurofilament data that was confounding because the response was maybe the exact opposite of what we would expect if we thought that there was any correlation in the data that was presented by the FDA. And we saw such a clean correlation in the Tofersen data.

So, it leaves us with questions of what might be working there. In general, with the clinical effectiveness, the data was there for one clinical trial. I think Dr. Alexander made the comment that it's unusual to go with just one trial. If you do, you hope that the data is compelling. It wasn't so compelling in this case. And in fact, there was a concern about mortality and the bulbar responses and how those results were looking, all of this was further stratified. The statistics was stratified in this floor effect concept. There seems to be a very disparate interpretation by the FDA and the sponsor in that regard. The FDA taking the position that such stratification was in essence an overanalysis and leads to potentially false interpretation. The sponsor trying to make the case that floor effect really does separate out subpopulations that are clinically meaningful.

However, when we looked at that data that we looked at the floor effect and it was separated out for placebo versus treatment. The placebo floor effect was not distinguishable and that makes it challenging because we don't understand the baseline progression of the disease to really understand how the floor might play a role in that. I think that is the essence of the conversation on multiple different fronts without recapitulating exactly everything that was said. I don't think that at this point, we will be taking comments from the sponsor related to this, but is there anyone from the committee that would like to add nuance to what I said? Or something I may have misrepresented in the chaos of trying to summarize or maybe misunderstood? Any comments from the committee? Dr. Fischbeck, please.

Dr. Fischbeck: I don't want to hog the mic here, but I just wanted to reiterate or voice my support for the comments by Dr. Gold and Dr. Lee in response to the comment by Kathleen O'Sullivan-Fortin about individual experience with the drug versus the experience in an organized study like this. And I think we, the FDA, and by extension, the members of this committee are charged with trying to give patients and prescribing physicians information about the safety and efficacy of a

product. And if we don't have it, then it's good to say that or, if the risk-benefit isn't quite what the sponsor would like it to be, we're supposed to say that also. And it's dangerous, heartfelt as these testimonies are, and I can really feel the pain having taken care of a number of ALS patients over the years, and I think that it really is a disease that needs a safe and effective treatment. And I think there are a lot of other prospects out there that we have encourage and approving one like this would get in the way of that.

Dr. Ahsan: Great. Thank you, Dr. Fischbeck and to remind me to actually summarize that part, even though it wasn't part of the discussion question, we heard some anecdotal stories that are an important perspective to hear. But we also did hear from Dr. Lee about being very thoughtful and not overly optimistic interpreting data, because that also comes at a cost. So, there's a lot to consider the opportunity costs, but then also potentially the cost of going down the wrong direction. Both of those are things to think about. Whether we move forward or whether we not. Dr. Shah.

Dr. Shah: Yeah, I'll just comment. I'm a cancer physician. And I think one of the comments that somebody made was that incremental change in ALS, maybe you should follow where the field is with cancer and just cancer in general, what we've learned over the years. I think what I am really struggling with is that I don't know that the underlying pathophysiology of ALS is understood well enough. And so, we're trying to come up and understand the mechanism of mesenchymal cells and this endotrophic factor, but there's just so many components that are unknown. And so, despite the preponderance of data, all of the biomarkers, I feel like we're left with a lot of uncertainties when you don't really know what it is that you're trying to do. And so, the functional outcomes to me, even if it is in a few patients, how do you weigh that? And so, I think that's something I will say that I am very much struggling with.

Dr. Ahsan: Thank you. That's a great point. These cell therapies are less well-characterized and understood than we would like and they're going in to treat a pathophysiologic condition that in this case is maybe less well understood than we would like as well. So, that does lead us with some quandaries. Dr. Gold.

Dr. Gold: Yeah just a quick comment to Dr. Shah. So, look you're right. We don't have a complete understanding of ALS. We don't have a complete understanding of depression and schizophrenia, but we still managed to get effective drugs out there. But when you don't have that kind of detailed knowledge and you want to address multiple pathological pathways at the same time, that's where it becomes really clear. You got to know exactly what it is you're giving.

Dr. Ahsan: Thank you.

Dr. Gold: We don't know and it's unclear that compounds that go after very single selective targets, other than these kinds of monogenic disorders like SOD-1. Right? That's an exception. But for sporadic ALS, these kind of multi-modal or multi-pathway approaches make sense. But like I said, you really have to understand what it is you're giving a patient.

Dr. Ahsan: Right. It's hard to work with two unknowns for sure.

Dr. Gold: So, they tell me. That was my first science lesson, right? Only modify one factor in an experiment, right?

Dr. Ahsan: Exactly. Scientific method comes back. Okay. So, I think we are running a little bit behind, but I do feel like everyone on the committee has gotten the chance to voice their opinions on this discussion question. There are no more raised hands. So, I think at this point, we need to go to the vote. Marie.

Ms. DeGregorio: Yes, when you are ready to proceed, we will.

Dr. Ahsan: Yes, I think we're ready to proceed to the vote.

Vote

Ms. DeGregorio: Okay. Sounds good. We're on the next slide. Thank you, everyone, and Dr. Ahsan. At this time, I will explain the voting process.

Only our 7 regular committee members and 12 temporary voting members, a total of 19 individuals, will be voting in today's meeting with respect to the voting process. Dr. Ahsan will read the voting question for the record. At this time, the FDA AV will move all non-voting members out of the main Zoom room. For those non-voting members in the Zoom room, please do not log out of Zoom. We will move you back into the main Zoom room in a few minutes after the voting is conducted. When only the voting members are present in the main Zoom meeting room, the chair will read the voting question again for the record. At this time, all voting members and temporary voting members will be asked to cast their vote by selecting one of the three voting options on their screen, which consists of yes, no, or abstain. To all voting members, you will have one minute to cast your vote after the question is read by the chair. Please note that once you have cast your vote, you may change your vote within the one-minute time frame before you press the submit button. Once the poll is closed, all votes will be considered final. Once all votes have been cast and non-voting members are put back into the main Zoom room, we will display the voting results and read the individual votes allowed for the public record. This process may take a few minutes and so before we start, does anyone have any questions related to the voting process?

Dr. Tuszynski: I'm sorry, where do we vote?

Ms. DeGregorio: We will provide a pop-up screen once all of the voting members are within the room minus any non-voting members. So, once we have you all arranged in the room as a group, AV will pop up a pop-up message and there will be radio buttons where you'll be able to

vote. So, it'll come up automatically. And if anyone has any trouble, just put it in the chat immediately, and then we'll work on a solution for you.

Dr. Tuszynski: Thank you.

Ms. DeGregorio: Alright. Okay. Dr. Ahsan, could you please read the voting question for the record?

Dr. Ahsan: So, the voting question is, do the data presented demonstrate substantial evidence of effectiveness for treatment of mild to moderate ALS? The options are A. Yes. B. No. C. Abstain.

Ms. DeGregorio: Okay, thank you. Okay we now need to prepare the Zoom room for the vote. Voting members and TVMs, please stay present. At this time, FDA AV will move all non-voting members out of the main room into a separate Zoom room. For those non-voting members in the Zoom room, please do not log out of Zoom. We'll move you back into the main Zoom room in a few moments once we're finished conducting and collating the vote.

Ms. DeGregorio: Okay. I think everyone's back. Welcome back. Thanks for being patient for that slight delay there. Okay, so we have a display of voting results. So, there are a total of 19 voting members for today's meeting. The results are one member voted yes. 17 members voted no. And one member abstained. Okay. So therefore, the voting question does not pass. Now next I'm going to wait for the queue of results to come up. Here we go. Okay, so you should see on the screen an Excel list of the voting responses of each voting member. I will read them aloud for the public record. Lisa Lee, no. Narali Shah, abstain. Jan Nolta, no. Ronald K. Liem, no. Joseph Wu, no. Nick Johnson, no. Rajiv Ratan, no. Andrew Buckley, no. Kathleen O'Sullivan-Fortin, yes. Donald Kohn, no. Lynn Raymond, no. Jun Li, no. Richard Kryscio, no. Wendy London, no.

Caleb Alexander, no. Mark Tuszynski, no. Gil Wolfe, no. Taby Ahsan, chair, no. Kenneth Fischbeck, no.

Okay, great. Thank you. This concludes the voting portion of today's meeting. Next slide, we begin with the committee vote explanation. Thank you.

Vote Explanations

Dr. Ahsan: Great. If you could put the Excel spreadsheet back up, alright Marie?

Ms. DeGregorio: Yeah, sure. That would be good too.

Dr. Ahsan: So, at this stage, we're going to go through each individual and they will have the opportunity to give the explanation for their vote. So, I'll take the prerogative of going last as chair, but we'll start at the top. Dr. Lisa Lee.

Dr. Lee: Thank you again. In my earlier comments, I think the data taken together do not provide enough substantial evidence. Not confusing, but conflicting information that was presented led to less clarity. And for the reasons I suggested in my previous comments, I voted no.

Dr. Ahsan: Thank you. Dr. Shah.

Dr. Shah: Yeah, so I'll echo to what I had said right before the vote. I think that there is just a fair amount of conflicting information that was presented today and a lot of emphasis on the mechanism of action for something that we don't entirely understand. And ultimately, the reason I abstained is I'm a little bit just worried that we're asking for the impossible and don't really know what it is that would be needed to be able to move this forward. And so, I struggle with just even the question. I was very compelled by the patients, but even more so, I was compelled by the providers who are taking care of these patients. Many who have decades of experience treating these patients. That leads me to believe that there is something there, but I don't know that it fits the regulatory platform that we currently have.

I think the CMC concerns are legitimate. But I also did not get any clarity on what it would be that it would take for a mesenchymal stem cell product to be approved. And so, I think that in ongoing discussions with the sponsor, those attributes really need to be understood. And so, I felt that I was not able to provide a vote.

Dr. Ahsan: Thank you, Dr. Shah. Dr. Nolta.

Dr. Nolta: Yes, I do work in the field of MSCs and I was very compelled by the patient's testimony. We always have responders and non-responders in the MSC field. I wanted to be able to approve this, but in the end, I just did not see the data there. I did not see overwhelmingly substantial evidence of effectiveness there and I just did not see the statistical data. So, at this point, I had to say no.

Dr. Ahsan: Thank you, Dr. Nolta. Dr. Liem.

Dr. Liem: Yeah, I too was very impressed and moved by the statements from the patients and their providers, but ultimately, I did not think the data was there. Therefore, I had to vote no.

Dr. Ahsan: Thank you, Dr. Liem. Dr. Wu.

Dr. Wu: Yeah, so I have to agree with the FDA scientists who did a great job in terms of presenting the data. I think, despite the patient's testimony, the data just doesn't substantiate the company's claims about efficacy. So, I voted no as well.

Dr. Ahsan: Thank you, Dr. Wu. Dr. Johnson.

Dr. Johnson: Like others said, very compelled by both the clinicians and the patient testimony. But unfortunately, the clinical data did not bear out the appropriate level of efficacy that would be required to move it forward. So, I had to vote no.

Dr. Ahsan: Thank you, Dr. Johnson. Dr. Ratan.

Dr. Ratan: I similarly was extremely moved by patients and their caregivers and just wanted to let them know there's a huge amount of hope in this field, that there's incredible amounts of science and actively moving towards patients going on, but I was not compelled by the clinical data presented or the evidence of quality control of the stem cells were target engagement and I voted no. I would encourage the company, I think that there are now many examples of the earlier you treat that there may be more opportunities for intervention. So, the company may be using a milder disease as a proxy for earlier, but maybe thinking about protonormal ALS. And a targeted population would be a reasonable next step.

Dr. Ahsan: Thank you, Dr. Ratan. Andrew Buckley.

Mr. Buckley: So, I looked at this through the lens of is this drug safe and is it effective? I didn't find that it was effective. It seemed to me like there's more evidence to the contrary. And then as to the issue of safety, it seems to me it's not as safe as maybe the sponsor would like it to be given the number of deaths in the neuron group versus the control group. As a person living with ALS, I certainly hope that should this drug ultimately not be approved, that the efforts made by the sponsor aren't for nothing. That there is some good that can come out of their studies to help move the ball down the field. But I'm very sensitive to approving a drug that may work on some people. I think that could ultimately result in more harm than good in the long run and set back the cause in general.

Dr. Ahsan: Thank you. Kathleen O'Sullivan-Fortin.

Ms. O'Sullivan-Fortin: Hi, this isn't a surprise. I voted yes. I think it is very clear that I include data that no one else considers as real data, which is obviously fine. I think there's no bigger risk than imminent certain death from ALS, and these are unique and desperate circumstances that would require us to exercise flexibility. I wish, with everyone else here, that

the sponsor's data was definitive and broad and fixed and helped and saved everyone. And it wasn't going to be that, but I still think there was a value.

Dr. Ahsan: Thank you. Dr. Kohn.

Dr. Kohn: Yes. So, I also want to mention once again, the FDA, I think, has done a very thorough detailed review. Really meticulously looking at the data. And of course, also I find the patient and family testimony was very compelling and we feel the pain that they're going through and the anecdotes of improvement. I hope those are true and I hope there is efficacy in there, but I think the substantial evidence of that effectiveness just wasn't there in the clinical data from the trials. So, I think based on that question, we had to vote no. And, I think one of the issues is the mechanism of action of the drug isn't clear whether it's anti-inflammatory, whether it's neurotrophins. And therefore, even the CMC issues that were discussed briefly of how you assess the potency of the drug product is difficult. So, I think those things need to be looked at. And then the right trial needs to be done to show efficacy.

Dr. Ahsan: Thank you, Dr. Kohn. Dr. Raymond.

Dr. Raymond: So, I voted no despite the compelling anecdotes and experiences, which I'm very sympathetic to. So, it's possible that this therapy has some benefit for some patients, but we look at the total when we have to decide whether this goes forward to public market, and there wasn't evidence that, for the whole group, this was effective. And there was evidence to potentially suggest it was actually deleterious, at least for those who are maybe more advanced with ALS causing more deaths, causing more bulbar dysfunction. So, for that reason, I would vote no. And to the last point about even if we had all the best evidence, if we don't have assurance that this effect, which may have worked for some people can be reproduced in a bigger market and a

bigger number of people because we know about the manufacturing process and how reliable it is, then we can't go forward either. So, both of those things made me vote no.

Dr. Ahsan: Thank you, Dr. Raymond. Dr. Li.

Dr. Li: Hi, as a physician, I see patients for the past more than 20 years, I would be thrilled if someone tell me there is a treatment effective for ALS. But unfortunately, what I see so far is not only that we don't have evidence for efficacy, but also, we have safety issues. And I'm particularly concerned about increased mortality in the treated arm, which is an independent influence of the floor effect that the company tried to make an argument on. And the mortality itself will not be affected by floor effect, but it's there. And it is quite concerning. And these two combinations just makes me really hard to say yes. So that's why I choose no.

Dr. Ahsan: Thank you, Dr. Lee. Dr. Kryscio.

Dr. Kryscio: Yes. I voted no, for several reasons. One is I felt that the data was not very strong. I was particularly concerned about the lack of efficacy in terms of survival and looking at all these different groups sizes and also compelled by the conversations we had from the clinicians who are on the panel and treat these patients. They didn't seem to think that this was a step forward. And although I will also reiterate that I have a very strong feeling for all the patients who are out there who are hoping for a cure for this disease because it is pretty bad. Thank you.

Dr. Ahsan: Thank you. Dr. Kryscio. Dr. London.

Dr. London: Yes, I voted no. I applaud the efforts of the applicant to seek an effective treatment for ALS and I found the testimonials compelling and moving. And so, I encourage the sponsor to identify a quality of life instrument that could capture this anecdotal benefit in an objective fashion and use it as a key secondary endpoint in a trial. I voted no because of the statistical evidence wasn't presented to me through regulatory requirement. The trial wasn't

designed or powered to detect the small treatment effect within the post hoc subgroup analysis of patients with an ALSFRS-R score greater than 35, and this was an exploratory analysis. It was post hoc and unplanned, uncontrolled type one error with an increased chance of a false positive result. The sponsor spent a lot of time examining the floor effect, and I think that this just adds evidence that the ALSFRS-R score is a poor endpoint, at least within the patients with the most severe disease to try and detect a treatment effect and perhaps should investigate a potential new primary endpoint.

Dr. Ahsan: Thank you, Dr. London. Dr. Alexander.

Dr. Alexander: Yeah, I voted no. I think the clinical evidence or lack thereof of clinical efficacy is actually quite clear and if you measure that up against statutory thresholds, I think it's a pretty clear call. I do think there is also a lot of additional uncertainty in my mind that was generated regarding the process, manufacturing process and quality controls. And, we talked about six or seven different important sources of uncertainty and open questions regarding, the consistency of the neurotrophic factor secretion. Dose to dose, person to person, across people, across different neurotrophic factors, the degree to which these persist in vivo. Whether they make it to the target area, how long they are there, and then all of those levels of uncertainty all can interact with each other as well. So, there's a second order and higher levels of uncertainty as well that I think just really complicate matters. So, I thought both the sponsor and FDA did careful jobs of making their case, but I think that the FDA has it right here with the concerns that they raised about this product at the current time.

Dr. Ahsan: Thank you, Dr. Alexander. Dr. Tuszynski.

Dr. Tuszynski: I also voted no. This was based on the absence of clear efficacy and the presence of potential harm. The exploratory analyses were marginal. And even with that, even if they were

valid, the effect sizes were extremely small or, as said by the sponsors, incremental. So, given the marginal nature of the analyses that were leading to potentially incremental changes, it just wasn't enough to get over the threshold.

Another issue was the absence of mechanism. If there are growth factors involved, they're extremely unlikely to reach the spinal cord parenchyma. And just for the whole program, it would be very nice to have a better concept of mechanism. Another issue was the poor manufacturing process and quality control substantiation in the documents that we saw. And I'd just like to say too that the presentations by the patients were just passionate and compelling. And my heart, like that of everybody else, goes out to the families and the patients that are dealing with this. And you never know if some independent patients aren't benefiting that it's possible that they are. But what's clear from these data is that for all comers to the trial, there was no evidence of an overall benefit and potential harm to non-responders. So, to approve this could be approving harm to the majority of patients who would enter the trial, even if there's a subset who are benefiting.

And finally, I bear in mind that approval of a marginal therapy impedes the progress of what's clearly needed at the end of the day, which are far better effective therapies than we have for ALS. Thank you.

Dr. Ahsan: Thank you, Dr. Tuszynski. Dr. Wolfe.

Dr. Wolfe: Yeah, as others have said, my heart bleeds for the ALS community. It's been a difficult day. The points that have been made about manufacturing, quality control, targeting, efficacy, and I'll add, I could not decipher a clear subset consistently going from what was seen in the Phase II studies to the Phase III studies with the various sub analyses. I just couldn't see it, of where it might work. And then the safety issues that have been raised. I voted no based on

that. We have some bunt singles in ALS. That's all we have. I've been dealing with ALS patients for 30 years. I won't even say they're clear singles using a baseball analogy. We've buned on the base, onto first base. I could not get a bunt single out of the data that was presented.

Dr. Ahsan: Thank you, Dr. Wolfe. Dr. Fischbeck.

Dr. Fischbeck: Yeah, I agree with what everybody else is saying. I can't really add to the list, including the comments by Kathleen O'Sullivan-Fortin. That's all important. And all the patients and family members who shared their stories with us. Maybe the only exception is what I picked up as a hint of negativity from Dr. Shah. I remain optimistic about the development of treatment, really safe and effective treatment for ALS. I hope that this experience helps further that goal which maybe this company can take the critical feedback and come back and design a trial, maybe even a small trial that does a good job of showing the safety and efficacy of this agent that that they believe in and that we would like to believe in too. Or it will just make room for other approaches. There are dozens, maybe hundreds of different drugs that are being developed now for ALS. And with so many shots on goal, I think I'm optimistic that some good will come. The truly effective patient treatment will be available to patients in the not too distant future.

Dr. Ahsan: Great, thank you, Dr. Fischbeck. So, I think I'll wrap up. The first thing I always remind myself and want to remind others is that we're not voting on a regulatory response. It is our job as part of this advisory committee to have a robust and dynamic conversation to help inform the FDA as they make their decisions forward. So, while I very much feel for the patients and this patient population. I think we all did, as Dr. Wolfe said, this was a tough day, listening to some of those stories is very compelling. And we want to do the best with what we can. But the question that was posed to us was the data presented demonstrate substantial evidence of effectiveness for treatment of mild to moderate ALS. And I felt that there was not enough data

presented that it was a bit of a missed opportunity by the sponsor and in their allocated time to discuss some of these issues related to the preclinical data related to the CMC.

It's tough to have a very clear mechanism of action at this early stage, but there was likely data that could have been presented to help make a more clean understanding of what we were proposing to do with this product. And the stratifying of the data, for me, the most compelling graph about the stratification was the fact that the floor effect placebo almost overlaid the no floor effect placebo. So, what were we stratifying? Were we really just stratifying data that supported the case versus not supported the case versus some sort of clinical group versus another, which is what we would really want to stratify on? I hope we end up with something for ALS and that is very effective in addition to the other drugs that have recently been approved. So, I really hope that we can move forward with something to treat these patients. But based on this question, I didn't see data presented by the sponsor that showed the effectiveness of this particular product.

Okay. So, with that, we do need to move forward to question three, which is if we can bring that question up. If the answer to voting question is no, please discuss potential designs for a trial to demonstrate substantial evidence of effectiveness for MSC-NTF for the treatment of mild to moderate ALS. So, I think there's been some question of should asking the FDA and sponsor what should the trial design be? This is the opportunity for the committee. To provide some input and some feedback to the sponsor and the FDA on those lines. And I think we also need to think about separating some hiccups in the execution during the COVID pandemic versus the actual clinical trial design and thinking about that. So, is there anyone on the committee that would like to start on proposing some elements of the clinical trial that they thought would be helpful? And I see Dr. Gold with his hand raised, please.

Dr. Gold: Yeah. So, a couple of quick ones. One is if you're really worried about a floor effect, and I agree with the notion that it's going to be difficult to develop a completely new instrument, but they're probably ways of doing it. Anyways, if you're going to use the current scale. And you're worried about a floor effect, you can either exclude people with any floor effect on any item where you can stratify, you can create strata or stratified randomization. So, attention to that. And certainly, if you know the baseline data, and you can work with blinded baseline data. You can follow the distribution of whatever the scores are and adapt your study if you want to. So, that's clearly one.

Number two, and it goes back to the point that I brought up. If the profile of the trophic factor production, that is subject is getting based on their own cells really strongly urge the sponsor to think about either standardization or grouping patients into groups where the profile of the trophic factor production looks like it's similar, right? So, you can't necessarily prespecify it in terms of how many groups there are, but if there's a way to actually sit there and say these patients were treated with cells that may, look like they're the same. So, some degree of grouping or clustering in the study, I think would help to manage a lot of kind of variability.

And then last, but not least, certainly the use of digital outcome measures to be able to get quality data, doesn't require patients to come to the clinic. Sleep emulation, voice analysis, all those kinds of things that would help us to get really granular data on either rate of progression or involvement of new domain. So, I think that there are methodological changes or methodological improvements that are already being used in other trials. So, I'll stop there. But thank you for letting me comment.

Dr. Ahsan: Yeah, no, that's very helpful. And I think that's the point of this point of the discussion, which is some tangible input to help with the clinical trial design. I think, if nothing else, a prospective statistical design will be very helpful. Dr. Fischbeck.

Dr. Fischbeck: Yeah. There are a number of things that came up in the discussion today that I think, as I said, I think the company could take to heart and design another trial that relies more on pre hoc rather than post hoc analysis and defining the patient population that they're going after and trying to tease out whether there is a real effect in the patients who called in or whoever sent their videos in today. Short of that, boy, my bias and it's easy to say and a lot harder to do would be to develop an allogenic rather than an autologous approach to MSC treatment for this disease. It would be hard to develop, but it would be and take time. Maybe it's something for another company to take on, but it would make this process a lot easier. It would help with standardizing the treatment and assessing its efficacy and safety in an organized way rather than having a different therapeutic product for each patient. So, that would be a recommendation. And it's easy to make recommendations, it’s a lot harder to carry them out.

Dr. Ahsan: Yeah, I think an allogenic product concept is a very disparate idea than this one. But I do like Dr. Gold's idea of, on an autologous product, where the primary raw material, which is the donor cells how that variability leads to variability in the end product using some product characterization to bin the product based on NTFs. And different categories would be very helpful to give a deeper analysis and really set the stage for if not having an MOI initially, starting to generate the data that will help inform an MOI at the end of that trial. Kathleen O'Sullivan-Fortin.

Ms. O’Sullivan-Fortin: Yeah, I appreciate the sponsor's attempts at inclusivity and not just cherry picking the healthiest newest patients. But in this case, it seems it didn't play out well.

And so, now that they know where they think they're going to get the best data, it's probably best to avoid the post hoc reframing and come back with a design that includes those folks. Also, I really struggled with the missing data and information about the manufacturing processes and so they need to have that locked down as part of the next go-around thanks.

Dr. Ahsan: Yeah, that's a great point, which is, unfortunately, if you design the trial for only certain populations, other patients don't get access, maybe a multi-arm approach might be something to think about. Dr. Li.

Dr. Li: I have been talking to our colleagues in our institution as well as other institutions and I have to say that the control, particularly the consistency of the MS cell production is a really big deal and is very challenging. And even we think the same subject, when you take the MS cell multiple times from the same patients, and then you manipulate them before they graft back to the subject. And to make sure that each batch of the cell has the similar quality. And even if only one of them had to compromise the quality and not only decrease the effectiveness, but also could even cause harm. I think I would really encourage that to not only just measure the sale viability and photosis, like what they have just presented. I think that paying attention to the consistency and also the biological substance products they produce from the cells and there's lots of other quality issues. And it's very important before the next trial. I think this is something that needs to be paid attention to.

Dr. Ahsan: Thank you, Dr. Li. That's a great import. Not just focusing on the expression profile of the NTFs, but also characterizing the MSCs can be of great import. Andrew Buckley.

Mr. Buckley: I just wanted to comment, respectfully suggest to the sponsor that they bring more focus to the front end, specifically the manufacturing process of the drug. I feel like that's an area where there is 100% control over the process and when that's not uniform across manufacturing

sites, it just raises very troubling questions just out of the gate in terms of the quality control of what's being produced. And as somebody who's a lay person that just really jumped out at me as being very detrimental to their ultimate goal, which is getting this drug approved. So, thank you.

Dr. Ahsan: Great. We are well past our time and we do still need to have some more comments from the FDA in terms of closing remarks. Potentially, those can keep up their hand if they really feel they would like to respond. Others, if it's something that we can move on from, perhaps you can remove your raised hand feature. Great. I appreciate everyone's willingness here. Great. Dr. Taszynski, please.

Dr. Taszynski: Just since this topic wasn't touched on, I would recommend narrowing the list of biomarkers that are measured in the future. And I mean pretty much the validated markers, neurofilament light, the others are not clear in ALS. And one might consider not including a bunch of others for definitive Phase III trial. And finally, I'd say stay consistent with how you give yourselves in the next trial be consistent with the Phase III instead of switching paradigms so you learn as much as you can while controlling variables that aren't being buried. Thank you.

Dr. Ahsan: Thank you. Yes. Very important for it to be a well-controlled, well-designed study. Dr. London.

Dr. London: Yes, my suggestion to the sponsor would be to add a key secondary endpoint or quality of life measure that would capture the anecdotal improvements in daily activities and capture the testimonials of benefit. Thank you.

Closing Remarks

Dr. Ahsan: Okay, great. Thank you very much everyone. Before I pass it off to the FDA for closing remarks, I do really want to appreciate everyone who has participated, the sponsor for their presentations, the FDA for their preparation and presentations, but also the patient population. It was very important to hear from you and the committee members who invested a

lot of time and effort, not only today, but in preparation for today. I hope that we had a nice, dynamic, robust discussion to help inform the FDA as they make their decisions moving forward. And so, with that, I pass it off to Dr. Witten, if she is still on the call. Let's see.

Dr. Witten: I still am on the call.

Dr. Ahsan: Thank you. Thank you.

Dr. Witten: First of all, I'd like to thank the advisory committee for the discussion, the attention to all these issues, which are all important for the vote and for their other recommendations. And I'll just mention that what we do, we'll be taking back the discussion and the recommendation and review the transcript. So, the advisory committee is just a recommendation. It's not a final FDA action. And as we also move towards completing the review, we will look at other material, including what's in the docket as was mentioned. I want to thank everyone else as you just did. Dr. Ahsan, I want to thank, in addition to the AC, the FDA staff who prepared for the meeting and worked at the meeting. I'd like to thank our speaker from the morning, members of the public who participated in the open public hearing as well as those who commented to the docket. We do at FDA recognize the need for treatments for this disease, it's a debilitating disease with an unmet need and we'll continue to work with all stakeholders. And now I think that Dr. Marks, our center director would like to say a word or two. So, I'm going to turn it over to him.

Dr. Marks: Yeah, no, thanks very much. First of all, I just want to thank all the members of the committee. Very much thank the open public hearing speakers. Thank the company for their presentation and thank the FDA presenters and the FDA advisory committee staff. Also, thanks Dr. Witten for doing a fantastic job organizing this meeting. We very much hear the needs of the ALS community. I think the patient testimony today was incredibly compelling about the need

for effective therapies. And obviously we'll go back from today and review the comments to the docket further and review the transcript from the meeting. And as Dr. Witten said put everything together. But I want to just say that the FDA does hear the tremendous need here for effective therapies in this space. And that's not lost on us. So, with that, I want to thank our chair and thank everyone for hanging in there through a long day. Really appreciate everyone's participation today. I'll turn it back over to the chair.

Adjournment

Dr. Ahsan: Great. I think we're at the end and I can, again, thank everyone. It's been a long day, but I think it was very fruitful. So, I'll pass it to Marie. Did you have some final comment before we do?

Ms. DeGregorio: Sure, I just want to thank you, Dr. Ahsan, Dr. Witten, and Dr. Marks. In closing, I want to thank this committee, CBER staff, including all AV staff for working so hard to make this meeting a successful one. I now call this meeting officially adjourned at 6:37 PM Eastern time. Have a wonderful evening. Thank you.