Food and Drug Administration
Center for Drug Evaluation and Research
Final Summary Minutes of the Peripheral and Central Nervous System Drugs Advisory Committee Meeting

Location: Please note that due to the impact of this COVID-19 pandemic, all meeting participants joined this advisory committee meeting via an online teleconferencing platform.

Topic: The committee discussed new drug application (NDA) 215887, for tofersen (BIIB067) intrathecal injection, submitted by Biogen Inc., for the treatment of amyotrophic lateral sclerosis (ALS) associated with a mutation in the superoxide dismutase 1 (SOD1) gene.

These summary minutes for the March 22, 2023 meeting of the Peripheral and Central Nervous System Drugs Advisory Committee of the Food and Drug Administration were approved on _4/21/2023____.

I certify that I attended the March 22, 2023 meeting of the Peripheral and Central Nervous System Drugs Advisory Committee (PCNS) of the Food and Drug Administration and that these minutes accurately reflect what transpired.

/s/	**/s/**
Jessica Seo, PharmD, MPH	Thomas J. Montine, MD, PhD
Designated Federal Officer, PCNS	Chairperson, PCNS

Final Summary Minutes of the Peripheral and Central Nervous System Drugs Advisory Committee Meeting
March 22, 2023

The Peripheral and Central Nervous System Drugs Advisory Committee (PCNS) of the Food and Drug Administration, Center for Drug Evaluation and Research, met on March 22, 2023. The meeting presentations were heard, viewed, captioned, and recorded through an online teleconferencing platform. Prior to the meeting, the members and temporary voting members were provided the briefing materials from the FDA and Biogen, Inc. The meeting was called to order by Thomas J. Montine, MD, PhD (Chairperson). The conflict of interest statement was read into the record by Jessica Seo, PharmD, MPH (Designated Federal Officer). There were approximately 1292 people online. There were a total of 26 Open Public Hearing (OPH) speaker presentations.

A verbatim transcript will be available, in most instances, at approximately ten to twelve weeks following the meeting date.

Agenda:

The committee discussed new drug application (NDA) 215887, for tofersen (BIIB067) intrathecal injection, submitted by Biogen Inc., for the treatment of amyotrophic lateral sclerosis (ALS) associated with a mutation in the superoxide dismutase 1 (SOD1) gene.

Attendance:

Peripheral and Central Nervous System Drugs Advisory Committee Members Present (Voting): Robert C. Alexander, MD; Liana G. Apostolova, MD, MSc, FAAN, Richard J. Kryscio, PhD; Michelle M. Mielke, PhD; Thomas J. Montine, MD, PhD (*Chairperson*)

Peripheral and Central Nervous System Drugs Advisory Committee Members Not Present (Voting): Merit E. Cudkowicz, MD

Peripheral and Central Nervous System Drugs Advisory Committee Member (Non-Voting): Michael Gold, MS, MD (*Industry Representative*)

Temporary Members (Voting): Klaus Romero, MD, MS, FCP; Tanya Simuni, MD, FAAN; David Weisman, MD; Michael Wilson (*Patient Representative*)

FDA Participants (Non-Voting): Teresa Buracchio, MD; Emily Freilich, MD

Designated Federal Officer (Non-Voting): Jessica Seo, PharmD, MPH

Open Public Hearing Speakers Present: Alison Burell; Raziel Green; Paul Melmeyer (Muscular Dystrophy Association); Robert Bucelli, MD, PhD; Senda Ajroud-Driss, MD; Cassandra Haddad; Peter Lawrence; Jean Swidler (Genetic ALS & FTD : End The Legacy); Larry Falivena; Connie M. Becker; Caroline Renko (PharmedOut); Abbi North; Blaine C.

Dangel; Chris Snow and Kelsie Snow; Lauren Webb, LCSW (Les Turner ALS Foundation); Tucker Olson (Olson ALS Foundation); Jessica Morris; Keith Mayl, MD, PhD; Brian Wallach and Sandra Abreyava; Todd Legg; Sarah Gascoigne; Calaneet Balas (ALS Association); Ravi Gupta, MD (Doctors for America); Reuben Mathew, MSPH; Julie Granning; Michelle Lorenz (Voices for ALS)

The agenda was as follows:

Call to Order	**Thomas J. Montine, MD** Chairperson, PCNS
Introduction of Committee and Conflict of Interest Statement	**Jessica Seo, PharmD, MPH** Designated Federal Officer, PCNS
FDA Introductory Comments	**Teresa Buracchio, MD** Director (Acting), Office of Neuroscience (ON) Office of New Drugs (OND), CDER, FDA
APPLICANT PRESENTATIONS	**Biogen, Inc.**
Introduction	**Toby Ferguson, MD, PhD** Vice President, Head of Neuromuscular Development Unit Biogen
Disease Background & Unmet Need	**Timothy M. Miller, MD, PhD** David Clayson Professor of Neurology Washington University
Efficacy	**Stephanie Fradette, PharmD** Clinical Development Lead and ALS Portfolio Head Biogen
Safety	**Laura Fanning, MD** Executive Medical Director, Global Medical Safety Biogen
Clinical Perspective	**Timothy M. Miller, MD, PhD**
Conclusion	**Stephanie Fradette, PharmD**
Clarifying Questions to the Applicant	
LUNCH	

FDA PRESENTATIONS

FDA Summary Presentations

Emily Freilich, MD
Cross-Discipline Team Lead
Deputy Director (Acting)
Division of Neurology 1 (DN1)
ON, OND, CDER, FDA

Tristan Massie, PhD
Biostatistics Reviewer
Division of Biostatistics 1
Office of Biostatistics
Office of Translational Sciences (OTS), CDER, FDA

Xiaohan Cai, PhD
Clinical Pharmacology Reviewer
Division of Neuropsychiatric Pharmacology
Office of Clinical Pharmacology (OCP)
OTS, CDER, FDA

Vishnu Sharma, PhD
Pharmacometrics Reviewer
Division of Pharmacometrics
OCP, OTS, CDER, FDA

Clarifying Questions to FDA

BREAK

OPEN PUBLIC HEARING

BREAK

Questions to the Committee/
Committee Discussion

ADJOURNMENT

Questions to the Committee:

1. **DISCUSSION:** Discuss whether the available evidence supports that a reduction in plasma neurofilament light chain (NfL) concentration observed in tofersen-treated patients with amyotrophic lateral sclerosis (ALS) secondary to a mutation in SOD1 (SOD1-ALS) is reasonably likely to predict clinical benefit for these patients.

   Committee Discussion*: The Committee was collectively in agreement that the available evidence supports that a reduction in plasma NfL concentration is reasonably likely to predict clinical benefit in SOD1-ALS patients treated with tofersen. Committee members acknowledged that while the placebo-controlled study did not meet any of its pre-specified endpoints, the data unequivocally demonstrated an effect on the SOD1 protein and a reduction of plasma NfL concentrations, resulting in a strong pharmacodynamic signal and suggesting decreased injury to neurons. Many members pointed out the context of a rare disease such as SOD1-ALS where another placebo-controlled trial would not be feasible and were in agreement that the totality of the evidence was sufficient to support a reasonably likely predictive benefit of reduction in plasma NfL concentrations. Please see the transcript for details of the Committee's discussion.*

2. **VOTE:** Is the available evidence sufficient to conclude that a reduction in plasma NfL concentration in tofersen-treated patients is reasonably likely to predict clinical benefit of tofersen for treatment of patients with SOD1-ALS?

   Vote Result: Yes: 9 No: 0 Abstain: 0

   Committee Discussion: *The Committee was unanimously in agreement that the available evidence was sufficient to conclude that a reduction in plasma NfL concentration in tofersen-treated patients is reasonably likely to predict clinical benefit of tofersen in the treatment of patients with SOD1-ALS. The Committee members cited reasons previously discussed in Question 1 as the rationale for their vote, with several members emphasizing the totality of the evidence was supportive of a reduction in plasma NfL concentrations as a biomarker or surrogate for clinical benefit. Please see the transcript for details of the Committee's discussion.*

3. **DISCUSSION:** Discuss the strengths and limitations of the available clinical data from the placebo-controlled study and long term extension regarding the effectiveness of tofersen for SOD1-ALS.

   Committee Discussion*: The Committee expressed agreement on the need for additional data to be able to conclude effectiveness of tofersen for the treatment of SOD1-ALS. There was a strong consensus that the placebo-controlled study failed to demonstrate evidence of tofersen's effectiveness for SOD1-ALS. However, many members agreed the data from the long-term extension study appears to be suggestive of tofersen's clinical effect, though not conclusive. A couple of members noted the limited number of events observed in the available data, and another member expressed concerns with the lack of a placebo group, as limitations of the long-term extension trial. Please see the transcript for details of the Committee's discussion.*

4. **VOTE:** Does the clinical data from the placebo-controlled study and available long-term extension study results, with additional supporting results from the effects on relevant biomarkers (i.e., changes in plasma NfL concentration and/or reductions in SOD1), provide convincing evidence of the effectiveness of tofersen in the treatment of patients with SOD1-ALS?

   Vote Result: Yes: 3 No: 5 Abstain: 1

   Committee Discussion: *A slight majority of the Committee members voted "No," agreeing that the clinical data from the placebo-controlled study and available long term extension results, with additional supporting results from the effects on relevant biomarkers (i.e., changes in plasma NfL concentration and/or reductions in SOD1), did not provide convincing evidence of effectiveness for tofersen in the treatment of patients with SOD1-ALS. These members cited the failure of the placebo-controlled trial to meet its pre-specified endpoints as the basis for their vote, with a couple of members noting the evidence presented meets the standards for accelerated approval, but not traditional approval.*

   The members who voted "Yes" acknowledged the difficulty of their decision and noted there were aspects of the data presented that suggested strong clinical evidence of tofersen's benefit. One member also cited the unmet need and seriousness of SOD1-ALS as a contributing factor to their decision, while another member expressed concerns about the financial burden for patients due to lack of payer coverage for tofersen if it were to be granted accelerated approval instead of full approval.

   The member who abstained cited the pre-competitive and non-competitive nature of his work as the reason for his abstention. Please see the transcript for details of the Committee's discussion.

5. **DISCUSSION:** Discuss the overall benefit-risk assessment for tofersen in patients with amyotrophic lateral sclerosis (ALS) secondary to a mutation in SOD1 (SOD1-ALS). If the available evidence supports a benefit, discuss if the risks appear to be acceptable given the observed treatment benefit. If the benefit-risk assessment does not appear favorable, discuss what additional data would be needed for the benefit-risk assessment to be favorable.

   Committee Discussion*: The panel members were in consensus that there was an overall positive benefit-risk profile for tofersen in patients with ALS secondary to a mutation in SOD1. Members acknowledged that while there were some serious neurologic adverse events reported in the studies, they appeared to be relatively infrequent and manageable. Some panel members noted that given the devastating nature of SOD1-ALS, patients would likely be willing to endure the treatment-associated risks, and other members pointed out some adverse events could be mitigated by ensuring proper training on drug administration. Therefore, the committee members were in agreement that the overall adverse event profile, in the context of the seriousness of the illness, was supportive of a favorable benefit-risk assessment for treatment of SOD1-ALS patients with tofersen. Please see the transcript for details of the Committee's discussion.*

The meeting was adjourned at approximately 5:31 p.m. ET.