Food and Drug Administration
Center for Biologics Evaluation and Research
Summary Minutes
75th Cellular, Tissue, and Gene Therapies Advisory Committee Meeting
September 27, 2023

Committee Members Tabassum (Taby) Ahsan, Ph.D. (Acting Chair) Marshall E. Bloom, M.D. + Christopher K. Breuer, M.D. + Eric Crombez, M.D. ** + Donald B. Kohn, M.D. Wendy B. London, Ph.D. Sean J. Morrison, Ph.D. + Melanie Ott, M.D., Ph.D. + Nirali N. Shah M.D., M.H.Sc. Gil I. Wolfe, M.D. Joseph Wu, M.D., Ph.D. **Temporary Voting Members** G. Caleb Alexander, M.D., M.S. Andrew Buckley, M.B.A., J.D. > Kenneth Fischbeck, M.D. Nicholas E. Johnson, M.D., M.S.C.I., F.A.A.N. Richard Kryscio, Ph.D. Lisa Lee, Ph.D. Jun Li, M.D., Ph.D., F.A.N.A., F.A.A.N. Ronald Liem, Ph.D. Jan Nolta, Ph.D. Rajiv R. Ratan, M.D., Ph.D. Lynn Raymond, M.D., Ph.D. Mark Tuszynski, M.D., Ph.D. **Industry Representative** Michael Gold, M.S., M.D. (Acting) ** **Consumer Representative** Kathleen O'Sullivan-Fortin, Esq. * +Not Attending * Consumer Representative ** Industry Representative >Patient Representative	**Guest Speaker** Evan Y. Snyder, M.D., Ph.D., F.A.A.P. **FDA Participants** Peter W. Marks, M.D., Ph.D. Celia Witten, Ph.D., M.D. (Speaker) Nicole Verdun, M.D. Leila P. Hann Rosa Sherafat-Kazemzadeh, M.D. (Speaker) Tom Finn, Ph.D. (Speaker) Xue (Mary) Lin, Ph.D. (Speaker) Gumei Liu, M.D., Ph.D. (Speaker) Xiaofei Wang, Ph.D. (Speaker) **Designated Federal Officers (DFO)** Marie DeGregorio LCDR Cicely Reese, Pharm.D. (Alternate) **Committee Management Officers (CMO)** LaShawn Marks Joanne Lipkind, M.S. (Alternate) **Committee Management Specialist (CMS)** Tonica Burke, B.S. **DSAC Director** Prabhakara Atreya, Ph.D.

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These summary minutes for the September 27, 2023, meeting of the Cellular, Tissue, and Gene Therapies Advisory Committee (CTGTAC) were approved on March 25, 2023.

I certify that I participated in the September 27, 2023, meeting of the CTGTAC meeting and that these minutes accurately reflect what transpired.

/s/	/s/
Marie DeGregorio	Tabassum (Taby) Ahsan, Ph.D.
Designated Federal Officer	Acting Chair

On September 27, 2023, the 75th meeting of the Cellular, Tissue, and Gene Therapies Advisory Committee (CTGTAC) took place in open session to discuss the biologics license application (BLA) 125782 from BrainStorm Cell Therapeutics, Inc. for debamestrocel (autologous bone marrow-derived mesenchymal stromal cells induced to secrete neurotrophic factors [MSC-NTF], NurOwn). The applicant has requested an indication for the treatment of mild to moderate amyotrophic lateral sclerosis (ALS). Given the topic of this meeting, it was determined to be a Particular Matter Involving Specific Parties (PMISP).

On September 27, 2023 at 10:00 a.m. Eastern Daylight Time (EDT), Dr. Taby Ahsan, the Acting Chair, called the meeting to order. The DFO, Ms. Marie DeGregorio, made administrative remarks, conducted roll call, invited the CTGTAC members and consultants to introduce themselves, and then read the Conflict of Interest (COI) statement into the public record. There was one conflict-of-interest waiver issued for the participation of Dr. Jun Li, a temporary voting member under 18 U.S. Code Section 208 in connection with this meeting. During the open session, the CTGTAC members, consultants, applicant, guest speakers, FDA speakers and staff, and public speakers all participated via Zoom web conference.

Dr. Celia Witten, Deputy Director of CBER, provided FDA Opening Remarks followed by brief Questions & Answers (Q&A).

Following the Q&A, Dr. Rosa Sherafat-Kazemzadeh, Clinical Team Leader in CBER's Office of Therapeutic Products (OTP), gave the FDA overview titled, "FDA Overview of BLA 125782, debamestrocel (MSC-NTF) for Treatment of Amyotrophic Lateral Sclerosis (ALS)."

Following the FDA overview, time was allowed for clarifying Q&A between the committee and Dr. Sherafat-Kazemzadeh.

Following the Q&A on FDA presentation, Dr. Evan Snyder, Director of the Center for Stem Cells and Regenerative Medicine at Sanford Children's Health Research Center, served as guest speaker and gave the presentation titled, "Some Guiding Principles When Contemplating Stem Cell-Based Approaches to Neurological Disease."

After his presentation, time was allowed for clarifying questions and answers between the committee and Dr. Snyder. This was followed by a committee break.

Once the committee returned from the break, the applicant team of speakers gave a presentation titled, "NurOwn for Treatment of ALS." The applicant presentations and speakers were as follows:

Introduction
- Stacy Lindborg, Ph.D.
- ALS Landscape and Unmet Need – Anthony J. Windebank, M.D.

Efficacy
- Phase 3 Results – Stacy Lindborg, Ph.D.
- Totality of Evidence in Prespecified ALSFRS-R in ≥ 35 Subgroup – Lee-Jen Wei, Ph.D.
- Supportive Clinical Evidence – Nathan Staff, M.D., Ph.D.
- Supportive Biomarker Evidence – Robert Bowser, Ph.D.
- Safety – Kirk Taylor, M.D.
- Benefit/Risk–Clinical Perspective – Anthony J. Windebank, M.D.

Following the applicant presentations, time was allowed for clarifying questions and answers between the committee and the applicant team of speakers listed above.

The committee was released for a 30-minute lunch. Once the committee returned from lunch, a 60--minute Open Public Hearing (OPH) session was held from 1:40 p.m. to 2:40 p.m. EDT in which 17 pre-registered public speakers made oral remarks; some of the pre-registered public speakers also gave PowerPoint presentations. The names of OPH speakers and their remarks may be obtained from the transcript posted on the CTGTAC website.

Following the OPH session, there was a brief committee break. Once the committee returned from the break, FDA staff gave a presentation titled, "BLA 125782, Application for debamestrocel (MSC-NTF) for Treatment of Amyotrophic Lateral Sclerosis (ALS)."

The FDA team of speakers was as follows:

- Dr. Tom Finn, BLA Chair and Chemistry, Manufacturing, and Controls Reviewer in OTP
- Dr. Gumei Liu, Clinical Reviewer in OTP
- Dr. Xue (Mary) Lin, Statistical Reviewer in the Office of Biostatistics and Pharmacovigilance
- Dr. Xiaofei Wang, Clinical Pharmacology Reviewer in OTP

Following the FDA speaker presentations, time was allowed for the committee to ask the FDA speakers some clarifying questions and receive answers, followed by a brief committee break.

Once the committee returned from the break, the Acting Chair began the committee discussion, voting, and vote explanation portion of the meeting. The committee started their discussion, addressing the first question that was displayed, followed by the DFO conducting the voting process on a single voting question. This was followed by a vote explanation by each voting member. Committee members then addressed the third question.

The following applicant proposed indication and three questions from FDA were presented to the committee:

Please note that the indication within the questions is different from the indication within the FDA Briefing Document. The applicant modified their proposed indication on September 22, 2023, from "treatment of amyotrophic lateral sclerosis (ALS)" to "treatment of mild to moderate amyotrophic lateral sclerosis (ALS)."

Questions for the Committee:

1. Please discuss the data presented in support of effectiveness for treatment of mild to moderate amyotrophic lateral sclerosis (ALS), including consideration of the mechanisms of action proposed by the sponsor, biomarker data including neurofilament data, and the clinical data.

Summary of Discussion: The committee members commented that if relying on data from a single clinical trial, the efficacy data should be compelling, and it was not in this case, for either proposed indication. While the Applicant proposed a floor effect concept, it appeared that the placebo floor effect was indistinguishable. The biomarker data was confounding for the single trial. There was also concern expressed regarding the safety data with more deaths reported in the treatment arm. The committee concurred that the mechanism of action for this product was not clear.

2. Voting question: Do the data presented demonstrate substantial evidence of effectiveness for treatment of mild to moderate ALS?

a) Yes
b) No
c) Abstain

The committee voting results were as follows: 1 Yes; 17 No; 1 Abstain.

At the completion of the voting, while the voting results were displayed, the DFO read the voting results for the public record.

Following the vote, the Acting Chair asked that all voting members explain their individual voting decisions, which they provided.

After the Committee discussion, voting, and vote explanation, committee members were asked to

address the third question.

3. If the answer to Question 2 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.

Summary of Discussion: The members who voted no agreed that the product should be well characterized and uniformly manufactured to ensure quality control issues discussed at this meeting will be addressed. Data to support a better understanding of the proposed mechanism of actions of anti-inflammatory or neurotrophic factor secretion would also improve trial design. The committee suggested a targeted population, measuring fewer biomarkers, perhaps limited to the validated ones, and identifying a quality-of-life instrument that could serve as a key secondary endpoint.

Following the committee discussion, Dr. Celia Witten thanked the committee and provided closing remarks.

The Acting Chair then handed the meeting over to the DFO who adjourned the meeting on September 27, 2023, at 6:37 p.m. EDT.

Additional meeting information and details may be obtained from the transcript, which may be viewed at:
Cellular, Tissue, and Gene Therapies Advisory Committee September 27, 2023 Meeting Announcement - 09/27/2023 | FDA.

The recording of the webcast of the meeting may be viewed at:
https://youtube.com/live/c-2-33ipSbk.