Individuals using assistive technology may not be able to fully access the information contained in this file. For assistance, please call 800-835-4709 or 240-402-8010, extension 1. CBER Consumer Affairs Branch or send an e-mail to: ocod@fda.hhs.gov and include 508 Accommodation and the title of the document in the subject line of your e-mail.

U.S. FOOD & DRUG ADMINISTRATION

Cellular, Tissue, and Gene Therapies Advisory Committee

FDA Overview of BLA 125782

debamestrocel (MSC-NTF) for
Treatment of Amyotrophic Lateral Sclerosis (ALS)

Applicant: Brainstorm Cell Therapeutics, Inc.

Rosa Sherafat, MD
Office of Clinical Evaluation
Office of Therapeutic Products
Center for Biologics Evaluation and Research, FDA

September 27, 2023

Overview

- Background
- Clinical Development of MSC-NTF
- Regulatory History of BLA 125782
- Overview of Today's Agenda

debamestrocel (MSC-NTF)

- MSC-NTF is a cell suspension composed of autologous, bone marrow-derived mesenchymal stromal/stem cells (MSC), cultured under conditions to increase neurotrophic factor secretion
- Route of administration: intrathecal injection
- Original proposed indication: treatment of amyotrophic lateral sclerosis (ALS)
- Revised indication [9/22/2023]: treatment of mild to moderate ALS

ALS: Rare, Fatal Neurodegenerative Disease

- Affects upper and lower motor neurons
- Progressive weakness of skeletal muscles
- 90% sporadic, 10% familial
- Prevalence: ~20,000 patients in US
- Life expectancy: 3 to 5 years after symptom onset due to respiratory failure
- Major unmet medical need

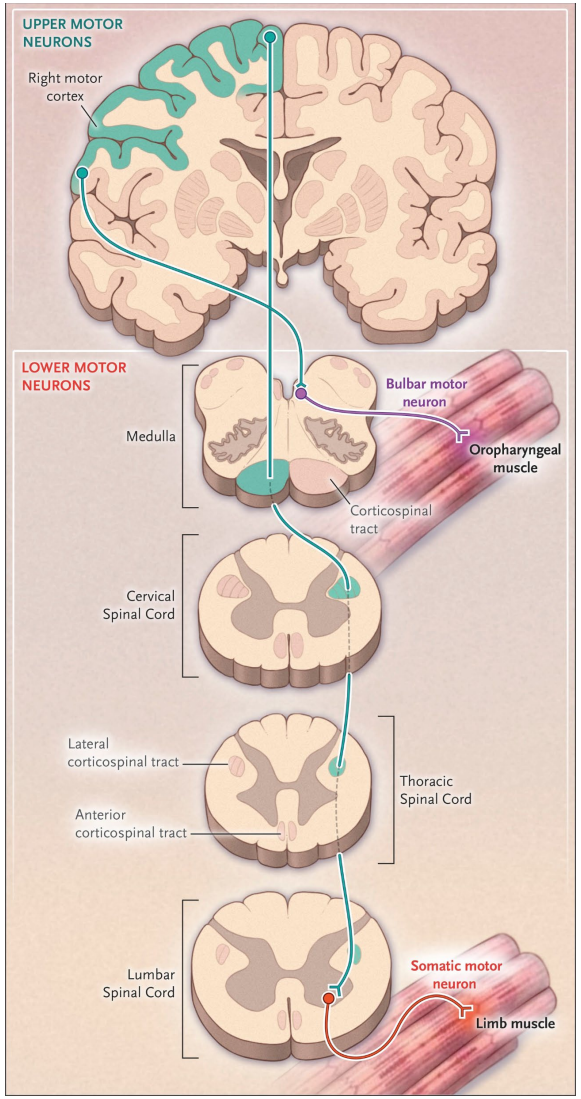

Image: *N Engl J Med* (2017) 377:162-172

Clinical Development of MSC-NTF

Early-Phase Studies

MSC-NTF-001-IL (N=12)

MSC-NTF-002-IL (N=14)

- Small, single-arm
- Several routes of administration

Phase 2 Study

BCT-001-US (N=48)

- Randomized, double-blind, placebo-controlled
- Single intrathecal and intramuscular administration

Phase 3 Study

BCT-002-US (N=196)

- Randomized, double-blind, placebo-controlled
- Intrathecal every 8 weeks × 3
- Final assessment at Week 28

BLA 125782 Regulatory History (I)

- Orphan Drug designation [2/4/2011]
- Fast Track designation [10/2/2014]
- Phase 2 study [2014-2016] results were not statistically significant
- Applicant selected population for Phase 3 study ("rapid progressors") based on findings from Phase 2 study
- Phase 3 study [2017-2020] failed to demonstrate statistically significant treatment difference on prespecified primary and secondary efficacy endpoints

BLA 125782 Regulatory History (II)

- BLA submission based primarily on exploratory subgroup analyses [9/9/2022]
- BLA submissions are expected to be complete, and to include all information needed for review
  - Upon receipt, FDA first performs a filing assessment
  - Filing means FDA has made a threshold determination that application is sufficiently complete to permit substantive review
- FDA issued Refuse to File letter for BLA 125782 [11/8/2022]

FDA CBER Standard Operating Policy and Procedure 8404: Refusal to File Procedures (www.fda.gov/media/111632/download)

Refuse to File BLA 125782 (I)

- **Available clinical data do not demonstrate substantial evidence of effectiveness for treatment of ALS**
  - Phase 3 study (BCT-002-US) failed to show efficacy for primary and all key secondary efficacy endpoints
  - Phase 2 study (BCT-001-US) also failed to show efficacy
  - Analyses of subgroups in the context of a negative study cannot provide evidence of effectiveness

Refuse to File BLA 125782 (II)

- **Chemistry, Manufacturing and Controls (CMC)**
  - Insufficient manufacturing information from clinical studies
    - Comparability of manufacturing
    - Consistency of manufacturing process
  - Substantial amount of missing or inadequate manufacturing information for proposed commercial process
    - Control of materials
    - Validation
    - Manufacturing consistency
    - Product stability
    - Facilities

BLA 125782 Regulatory History (III)

- **Paths forward discussed with the Applicant**

1. Submit a new BLA containing all necessary information, including information identified in the refuse-to-file letter. FDA noted the requirements to
   - generate evidence of effectiveness, and evidence of safety, from adequate and well-controlled clinical investigations
   - submit a complete Chemistry, Manufacturing and Controls module with all necessary validation studies completed, and
   - have commercial manufacturing facilities that are ready for inspection

OR

2. Request that BLA 125782 be filed over protest

BLA 125782 Regulatory History (IV)

- **File over protest**
  - Applicant chose to File Over Protest [2/7/2023]
  - Applicant voluntarily submitted the following:
    - Exploratory post-hoc subgroup analyses of clinical data
    - Exploratory analysis of biomarker data
    - Additional CMC information
- **Modified proposed indication**
  - Applicant modified the proposed indication from treatment of ALS to treatment of mild to moderate ALS [9/22/2023]

Overview of Today's Agenda

10:50 am	**Guest Speaker Presentation (40 min, including 10 min Q & A)** Evan Snyder MD, PhD Director, Center for Stem Cells and Regenerative Medicine Sanford Children's Health Research Center, La Jolla, CA
11:40 am	**Applicant Presentation: Brainstorm Cell Therapeutics (85 min, including 15 min Q & A)**
1:05 pm	**Lunch (35 min)**
1:40 pm	**Open Public Hearing (60 min)**
2:50 pm	**FDA Presentation (85 min, including 15 min Q & A)**
4:15 pm	**Committee Discussion, Voting, and Vote Explanation (100 min)**
5:55 pm	**Closing Remarks (5 min)** Celia Witten, MD, PhD Deputy Director, CBER, FDA
6:00 pm	**Meeting Adjourned** Marie DeGregorio, BA Designated Federal Officer, FDA

FDA Presentation: Key Points

- Critical manufacturing controls not in place and/or incomplete, precluding substantive review
- Adequate product quality not established
- Both randomized, double-blind, placebo-controlled studies failed to show efficacy
- Survival results are limited and unfavorable
- Subgroup analyses are exploratory
- Biomarker analyses do not indicate clear association between any assessed biomarker and clinical benefit

Discussion and Voting Questions

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 Applicant, biomarker data including neurofilament data, and the clinical data.

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

3. If the answer to the Question 2 is no, please discuss potential designs for a trial to demonstrate substantial evidence of effectiveness for MSC-NTF for treatment of mild to moderate ALS.

Thank You!