Debamestrocel (MSC-NTF, NurOwn; Brainstorm Cell Therapeutics) has not demonstrated effectiveness as a treatment for Amyotrophic Lateral Sclerosis (BLA 125782)

Testimony before the Food and Drug Administration's Cellular, Tissue, and Gene Therapy Advisory Committee

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I'm Michael Abrams from Public Citizen's Health Research Group. I have no financial conflicts of interest on this matter.

The analysis conducted by Food and Drug Administration (FDA) scientists shows that debamestrocel (autologously transplanted mesenchymal stromal cells engineered to secrete increased levels of neurotrophic factors, MSC-NTF) has yet to demonstrate effectiveness as a treatment for amyotrophic lateral sclerosis (ALS).[1] The single phase 3 trial for this biologic drug (BCT-002-US) failed to meet any of its pre-specified primary or secondary endpoints.[2] Moreover, bio-assay studies failed to show drug-induced cerebral spinal fluid (CSF) concentrations that logically connect treatment with MSC-NTF to laboratory values of neuronal biomarkers and motor function in patients. The FDA additionally has not been able to verify that MSC-NTF can be reliably manufactured.[3]

In the 28-week phase 3 study, 189 participants were randomized to MSC-NTF or placebo. The study did not show a significant difference between the groups in the proportion of responders to the biologic drug, which was the primary efficacy endpoint.[4] Six secondary endpoints were similarly negative for efficacy.[5]

There were 10 deaths in the MSC-NTF group and 3 in the placebo group.[6] Using a Kaplan-Meier analysis, this difference between groups was significant.

After-the-fact analyses by the sponsor found that a subsample of the highest functioning participants at baseline were significantly more responsive to the MSC-NTF than to placebo.[7] Such a *post-hoc* finding, however, was clearly biased towards a false-positive result, and was

[1] FDA briefing document. BLA 125782. Drug name: debamestrocel (MSC-NTF, NurOwn). Applicant: Brainstorm Cell Therapeutics. Cellular, Tissue, and Gene Therapy Advisory Committee Meeting. September 27, 2023. https://www.fda.gov/media/172403/download. Accessed September 25, 2023. PDF p. 7.
[2] *Ibid*. PDF p. 8.
[3] *Ibid*. PDF pp. 8, 19.
[4] *Ibid*. PDF p. 33.
[5] *Ibid*. PDF p. 33.
[6] *Ibid*. PDF p. 8.
[7] *Ibid*. PDF p. 9.

invalidated by the FDA-review showing that there was no evidence of a sponsor-hypothesized "floor effect" regarding motor function declines from baseline through week 28.[8]

Laboratory assays and facility inspections have yet to verify the quantity and central nervous system dispersion of cells and tropic factors delivered with each injection.[9]

Although CSF sampling up to 20 weeks after the first MSC-NTF treatment did identify some biomarkers (for example, neurofilament protein, vascular endothelial growth factor) suggesting that the biologic drug protects neurons,[10] those analyses were plagued by missing data in approximately half of the sample, and the levels of the biomarkers were mostly not correlated with functional outcomes.[11]

We thus agree with the FDA that this biologics license application 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 treatments for ALS, the application fails to provide reasonable evidence of the drug's effectiveness and safety.

Thank you.

[8] *Ibid*. PDF p. 39.
[9] *Ibid*. PDF pp. 18, 19, 20, 21.
[10] *Ibid*. p. 21.
[11] *Ibid*. PDF p. 9.