BrainStorm Cell Therapeutics Data Show Treatment with NurOwn Significantly Reduces NfL, a Key Biomarker of Neurodegeneration

New data presented this week at Gordon Research Conference

Analysis reinforces NfL levels as predictive of ALS clinical outcomes

NEW YORK, July 7, 2023 /PRNewswire/ -- BrainStorm Cell Therapeutics Inc. (NASDAQ: BCLI), a leading developer of adult stem cell therapeutics for neurodegenerative diseases, this week presented new biomarker data from the Phase 3 trial of its late-stage investigational ALS treatment, NurOwn at the 2023 ALS and Related Motor Neuron Diseases Gordon Research Conference. These data show that treatment with NurOwn significantly elevated markers of neuroprotection and lowered markers of neuroinflammation and neurodegeneration, including neurofilament light (NfL) over time compared to placebo in all trial participants.

New data analysis presented this week was motivated by the regulatory precedent set by a recent FDA drug approval in ALS, and the knowledge gained through the regulatory process, suggesting that the blood-based biomarker neurofilament light (NfL) is associated with disease prognosis and progression in patients with ALS and potentially other neurodegenerative diseases. It is believed that reductions in plasma NfL are reasonably likely to predict clinical benefit in ALS.

"It's well known that in ALS, accounting for disease characteristics such as site of onset, time from first symptom to treatment and baseline physical function are important to understanding the treatment effect in clinical trials given the great heterogeneity in the disease, which can influence prognosis," said Stacy Lindborg, PhD, BrainStorm co-CEO and presenter of the poster. "The data we presented at the Gordon Research Conference show that it is equally important to examine biomarker data, particularly neurofilament light, which is a predictor of disease progression. Treatment-driven reductions in NfL are associated with better clinical outcomes in ALS."

About the data analysis

The presentation, titled "CSF biomarkers identified as predictive of clinical outcomes in ALS participants following NurOwn treatment in a phase 3 clinical trial: Reductions in NfL associated with less ALSFRS-R decline", examined biomarkers that were pre-specified in the NurOwn study: 16 pro-inflammatory/anti-inflammatory, eight neurodegeneration, and nine neuroprotection biomarkers. This analysis is the largest biomarker study conducted in people living with ALS. Cerebrospinal fluid was collected for all participants in the trial seven times, per the protocol. The data provide further evidence of the importance of NfL as a prognostic and predictive biomarker. The addition of baseline disease covariates and additional biomarkers to NfL encompassing inflammation and neuroprotection more fully explains the clinical response to NurOwn observed in the trial.

The poster presentation is available on the BrainStorm website, on the Events & Presentations section:https://ir.brainstorm-cell.com/events-and-presentations

Highlights of the biomarker analysis:

- Statistical modeling identifies three biomarkers that predict clinical outcomes observed with NurOwn-treatment in the Phase 3 trial (BCT-002), including change in Galectin-1 and baseline biomarkers NfL and LAP/TGFβ1, highlighting the importance of three pathways important to ALS in the observed clinical outcomes.
- Baseline disease characteristics pre-specified in the primary efficacy model were included as covariates in the statistical analysis of biomarker data, following 2023 FDA guidance and ALS industry standard. These covariates were all found to be important in the analysis of clinical outcomes ($p<.001$, each covariate), in addition to biomarker data.
- Accounting for baseline disease covariates, NurOwn treated participants had reduced NfL values from baseline to week 20 compared to placebo ($p<0.05$).
- NfL baseline levels were prognostic of ALS disease progression, confirming results from other ALS trials. Participants with greater decline from baseline at week 28 as measured by ALSFRS-R total score, had higher baseline NfL values, $r=-0.33$, $p=0.0064$.
- Causal Inference using a natural disease progression model showed a relationship between reductions due to NurOwn in NfL changes from baseline and ALSFRS-R changes from baseline. The correlation between NurOwn-driven changes at the final measure in NfL (week 20) and ALSFRS-R (week 28), after adjusting for the predicted changes due to natural disease progression, was $r=-0.365$, $p=0.087$. This analysis was conducted in participants who had all ALSFRS-R items >1 at baseline.

About NurOwn®

The NurOwn® technology platform (autologous MSC-NTF cells) represents a promising investigational therapeutic approach to targeting disease pathways important in neurodegenerative disorders. MSC-NTF cells are harvested from each person with ALS and are manufactured using an innovative and proprietary process to secrete neurotrophic factors to target specific neurodegenerative diseases. The lead program for NurOwn is for the treatment of ALS, which is under FDA review. BrainStorm's long-term commitment to ALS is demonstrated in preclinical research and a series of clinical studies, all of which have been published in peer-reviewed journals.

The Phase 3 pivotal trial NurOwn did not reach statistical significance on the primary or secondary endpoints, likely due to a "floor effect," which confounds measurement of disease progression in patients with more advanced disease. A thorough analysis of NurOwn Phase 3 data shows evidence of clinically meaningful effectiveness in ALS participants who have not progressed to advanced levels of disease progression. In a pre-specified group of participants with an ALSFRS-R score ³35, there was a larger treatment effect across all endpoints with NurOwn compared to placebo, which aligned with historical trials and the study power assumptions. With a statistically significant difference on a key endpoint (change from baseline in ALSFRS-R). Additionally, a post-hoc sensitivity analysis of patients across threshold of >26 through ≥35 on the ALSFRS-R highlighted that NurOwn-treated patients retain, on average, two points of function more compared to placebo -- clinically meaningful preservation and important for quality of life for a person living with ALS and their loved ones.

NurOwn's clinical program also included the largest cerebrospinal fluid (CSF) biomarker study ever done in ALS, strong and consistent biomarker data, which are predictive of clinical response in the trial, span pathways that are important to ALS (neuroinflammation, neurodegeneration, neuroprotection), and align with NurOwn's mechanism of action. Biomarker data in all trial participants showed consistent biological patterns of NurOwn reducing markers of inflammation and neurodegeneration and increasing neuroprotective markers relative to placebo. Biomarker patterns were consistent across all NurOwn-participants, including in those with Advanced ALS disease where clinical scales, such as the ALS Functional Rating Scale, have demonstrated measurement challenges. Three CSF biomarkers were predictive of clinical outcomes in NurOwn-treated participants– neurofilament light (NfL), galectin-1, latency associated peptide of TGF-beta1 (LAP or TGF-b).

The NurOwn clinical program has generated valuable insights into the pathology of ALS, as well as disease progression and treatment. Since the initial Phase 3 readout, BrainStorm has shared the full dataset through rigorous peer-reviewed analysis, including: quantification of Floor Effect, which had been noted but never before explored in depth; evaluation of multiple pre-specified biomarkers, collected at seven different points across 20 weeks during the trial, allowing a longitudinal view; and analysis of genetic data, which represents one of the first ALS trials to prospectively invoke pharmacogenomic analysis of clinical outcome, offering great promise for the development of future treatments for ALS.

BrainStorm previously announced the FDA intension to hold an ADCOM meeting to review NurOwn for the treatment of ALS. The company filed a BLA for NurOwn on September 9, 2022, and received a Refusal to File (RTF) letter from FDA on November 8, 2022. Following a Type A meeting and subsequent discussions with the FDA BrainStorm requested that CBER utilize the FDA's "File Over Protest" procedure, which offers the shortest amount of time to complete the regulatory process. The BLA was filed over protest, allowing completion of the regulatory process in the shortest time possible, and active review resumed on February 7, 2023.

About BrainStorm Cell Therapeutics Inc.

BrainStorm Cell Therapeutics Inc. is a leading developer of innovative autologous adult stem cell therapeutics for debilitating neurodegenerative diseases. The Company holds the rights to clinical development and commercialization of the NurOwn® technology platform used to produce autologous MSC-NTF cells through an exclusive, worldwide licensing agreement. Autologous MSC-NTF cells have received Orphan Drug designation status from the U.S. Food and Drug Administration (FDA) and the European Medicines Agency (EMA) for the treatment of amyotrophic lateral sclerosis (ALS). BrainStorm has completed a Phase 3 pivotal trial in ALS (NCT03280056); this trial investigated the safety and efficacy of repeat-administration of autologous MSC-NTF cells and was supported by a grant from the California Institute for Regenerative Medicine (CIRM CLIN2-0989). BrainStorm completed under an investigational new drug application a Phase 2 open-label multicenter trial (NCT03799718) of autologous MSC-NTF cells in progressive MS and was supported by a grant from the National MS Society (NMSS).

Safe-Harbor Statement

Statements in this announcement other than historical data and information, including statements regarding BrainStorm's Type A meeting with the FDA and the clinical development of NurOwn® as a therapy for the treatment of ALS, constitute "forward-looking statements" and involve risks and uncertainties that could cause BrainStorm Cell Therapeutics Inc.'s actual results to differ materially from those stated or implied by such forward-looking statements. Terms and phrases such as "intend," "should," "could," "will," "believe," "potential," and similar terms and phrases are intended to identify these forward-looking statements. The potential risks and uncertainties include, without limitation, management's ability to successfully achieve its goals, BrainStorm's ability to raise additional capital, BrainStorm's ability to continue as a going concern, prospects for future regulatory approval of NurOwn®, whether BrainStorm's future interactions with the FDA will have productive outcomes, the impacts of the COVID-19 pandemic on our clinical trials, supply chain, and operations, and other factors detailed in BrainStorm's annual report on Form 10-K and quarterly reports on Form 10-Q available at http://www.sec.gov. These factors

should be considered carefully, and readers should not place undue reliance on BrainStorm's forward-looking statements. The forward-looking statements contained in this press release are based on the beliefs, expectations, and opinions of management as of the date of this press release. We do not assume any obligation to update forward-looking statements to reflect actual results or assumptions if circumstances or management's beliefs, expectations or opinions should change, unless otherwise required by law. Although we believe that the expectations reflected in the forward-looking statements are reasonable, we cannot guarantee future results, levels of activity, performance, or achievements.

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