An Overview of The Phase 3b Clinical Trial of Debamestrocel in ALS

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Background

Amyotrophic lateral sclerosis (ALS) is a devastating neurodegenerative disease affecting the motor neurons, leading to progressive muscle weakness, paralysis, and ultimately death. Debamestrocel (MSC-NTF; NurOwn®) cell therapy is based on treatment with autologous, bone marrow-derived mesenchymal stem cells (MSCs), which are enriched, propagated ex-vivo, and induced to secrete neurotrophic factors (NTFs) such as glial-derived growth factor (GDNF), brain-derived neurotrophic factor (BDNF), vascular endothelial growth factor (VEGF), galectin-1, and hepatocyte growth factor (HGF).

BrainStorm Cell Therapeutics completed a large, randomized, placebo-controlled, Phase 3 clinical trial of NurOwn® in ALS participants (n=189) to evaluate the efficacy and safety of 3 repeated intrathecal (IT) doses of NurOwn every 8 weeks (Cudkowicz et al. 2022). While the trial did not reach statistical significance on its primary endpoint (a novel endpoint based on the responder analysis of change in the rate of decline in post-treatment vs pre-treatment slope in ALSFRS-R), the data provides valuable insights and guidance for future trials.

Positive data from multiple subgroup analyses in early disease shows meaningful and nominally significant treatment benefit across multiple endpoints and over time. This has informed the design of this phase 3b clinical trial in participants with mild-moderate ALS. the FDA for a Special Protocol Assessment (SPA) agreement.

Clinical Trial Objectives

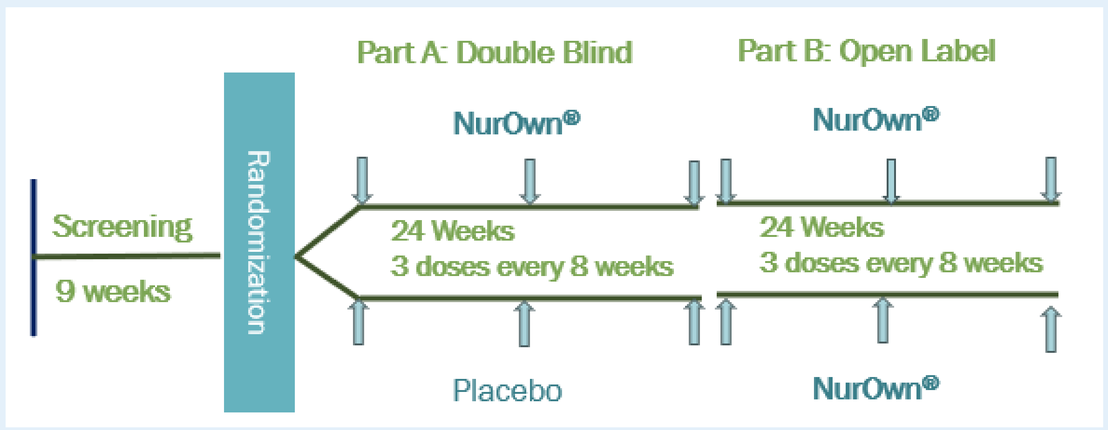
- NurOwn's phase 3B clinical trial in ALS (BCT-006-US) is designed as a pivotal registrational trial to support the application for regulatory approval of NurOwn as a treatment for mild-to-moderate ALS.
- The primary objective of this Phase 3B clinical trial is to evaluate the efficacy of NurOwn® compared to placebo in the treatment of participants with ALS based on the Revised Amyotrophic Lateral Sclerosis Functional Rating Scale (ALSFRS-R).

Clinical Trial Design

BCT-006-US is double-blind, placebo-controlled phase 3B clinical trial of NurOwn® in ALS that includes 2 parts:

- Part-A is a double blind, placebo controlled period of 24 weeks duration. Up to approximately 200 participants are planned to be enrolled and randomized 1:1 to NurOwn® and placebo groups. Following informed consent, a 6-8 weeks screening period will allow eligible participants to undergo a single bone marrow aspiration procedure to isolate the mesenchymal stem cells (MSCs). MSCs will then be propagated for approximately 2 weeks, and cryopreserved. Approximately 10 days prior to each IT dose administration, MSCs will be thawed, propagated, and induced into MSC-NTF cells (NurOwn®). MSC-NTF cells or placebo are administered via 3 repeated intrathecal injections, once every 8 weeks.
- Part-B is an open-label extension period of 24 weeks duration. All eligible participants who complete Part-A will have the option of entering Part-B to receive MSC-NTF cells or placebo via 3 repeated intrathecal injections, once every 8 weeks.
- An independent Data Monitoring Committee (DMC) will monitor the safety of the participants.

Study Schema



Select Entry Criteria & Outcome Measures

Entry Criteria

- Early onset: < 2 years from 1st symptom
- ALSFRS-R: ALL items ≥ 2
- ALSFRS-R total score ≤ 45
- SVC ≥ 65%
- El Escorial: Laboratory-supported probable, probable, or definite (no "possible")

Size/Power:

- N= 200 / 85-95% Power

Endpoints

- Primary Endpoint: @ Week-24 (end of Part A)
  - ALSFRS-R change from baseline
  - P-value: primary inference from CAFS
- Secondary and exploratory endpoints:
  - SVC, HHD
  - Survival
  - PROs: ALSAQ-40, Zarit caregiver burden
  - Biomarkers, e .g. NfL

Regulatory Milestones

De-risked Phase 3b Registrational Trial

Enroll the right population: ALS patients who are early in the disease process

Rigorous entry criteria

Defined primary endpoint: ALSFRS-R score change from baseline to week 24

Enhanced statistical power

FDA SPA agreement secured in April 2024
Fast Track designation
Orphan Drug designation

Eligibility Criteria

Up to approximately 200 participants with early and mild-moderate ALS will be allowed to enter Part-A to receive either NurOwn® or Placebo, while being allowed to also receive concomitant treatment of an approved standard of care (e.g., riluzole, edaravone, tofersen).

Key entry criteria include:

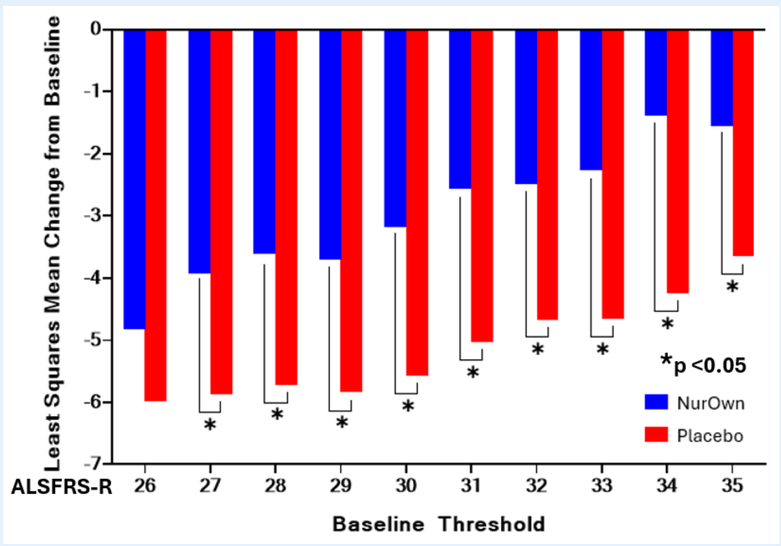
- Male and female participants 18 to 75 years old
- ALS diagnosis defined by the revised El Escorial criteria as laboratory-supported probable, clinically probable, or definite
- Early disease: having had first ALS symptom(s) within the prior 24 months
- ALSFRS-R: ALL items ≥ 2
- ALSFRS-R total score ≤ 45
- Upright Slow Vital Capacity (SVC) ≥65% of predicted for gender, height, and age
- Negative test for Hepatitis B, Hepatitis C, human immunodeficiency virus (HIV)
- No prior stem cell therapy
- No active participation in any other ALS interventional study
- Able to tolerate the IT cell treatment, bone marrow biopsy, and other study procedures
- No history of cancer or any medical, neurologic or autoimmune disease that may confound the study

NurOwn Phase 3 Trial in ALS – Results in Mild-Moderate ALS

Change from Baseline to Week 28 in ALSFRS-R Total Score across subgroups with baseline ALSFRS-R thresholds that range from ≥26 to ≥35.

Over ~2 points benefit in function at Week 28 consistently observed across thresholds above 27, indicating treatment benefits for participants who were at earlier stage of the disease.

Figure - 1



Nominal p values

Mechanism of Action

Debamestrocel, autologous MSC-NTF cells, are injected directly into the spinal fluid, in close proximity to the damaged motor neurons in ALS, to facilitate healing and repair.

Debamestrocel MSC-NTF cells have the capacity to offer dual therapeutic benefits of:

- MSCs: promote neurogenesis, modulate neuroinflammation, and contribute to neuroprotection
- NTFs (Neurotrophic Factors): enhance neuronal survival and function

Assessments

Efficacy Assessments

- ALSFRS-R: 4 functional domains including Bulbar, Fine Motor, Gross Motor, and Respiratory
- CAFS (Clinical Assessment of Function & Survival): ranks the participants' clinical outcomes based on survival time and change in ALSFRS-R score
- SVC (Slow Vital Capacity): a measure of respiratory function based on the maximum amount of air a participant can exhale in a single breath
- HHD (Hand-Held Dynamometry): quantifies muscle strength via a portable measurement device
- ALSAQ-40: patient-reported outcome that measures 5 areas of health status: Eating and Drinking, Communication, Activities of Daily Living & Independence, Physical Mobility, and Emotional Functioning
- ZBI (Zarit Burden Interview): measures the burden experienced by caregivers by assessing their perceptions of burden that impacts their health, personal, social, or financial well-being

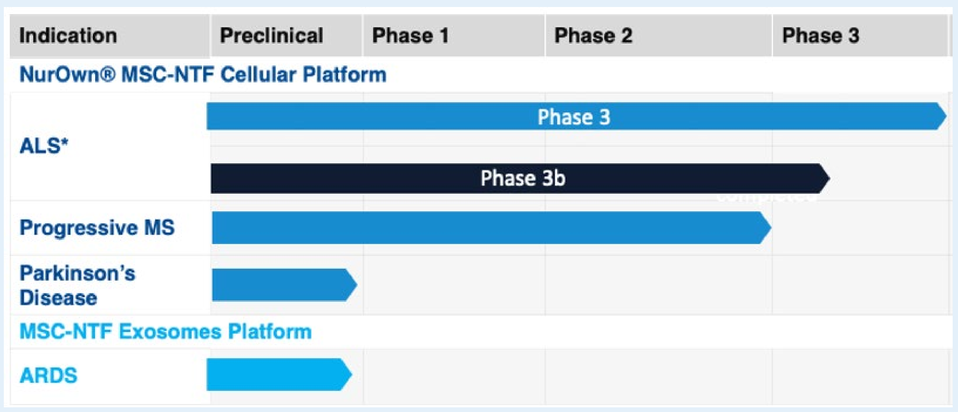
Biomarker Assessments

- CSF and blood samples are optionally collected for analysis of biomarkers of neuroinflammation, neurodegeneration, and neuroprotection

Genetic Assessments

- Buccal (cheek) sample using an oral swab is optionally collected for DNA evaluation of ALS-related genes and single nucleotide polymorphisms

About BrainStorm Cell Therapeutics - Portfolio



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