Design of A Phase 3B Trial of Debamestrocel (NurOwn®) 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). The trial enrolled an unexpectedly large number of participants with advanced ALS at the start of the study (23%), and did not meet the novel primary endpoint based on the responder analysis of change in the rate of decline in post-treatment vs pre-treatment slope in ALSFRS-R.

Positive data from multiple subgroup analyses, including the prespecified subgroup of participants with baseline ALSFRS-R total score of ≥ 35 (Figure-1), informed the design of this phase 3B clinical trial in participants with mild-moderate ALS that is currently under review with 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

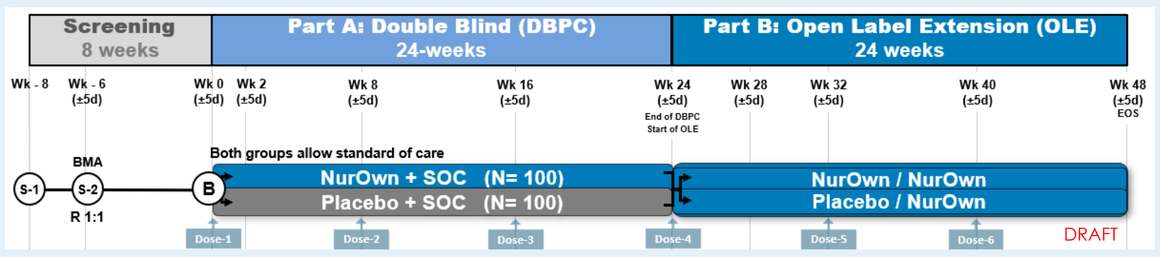
BCT-006-US is double-blind, placebo-controlled phase 3B clinical trial of NurOwn® in ALS that includes 2 parts:

- 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.

Schema: under review by FDA



B = Baseline; BMA = bone marrow aspiration; d = day; DBPC = double blind placebo controlled; OLE = open-label extension
S-1 = Screening Visit 1; S-2 = Screening Visit 2; SOC = standard of care; R = randomization; Wk = Week

Schedule of Activities

	Screening Period		Part A: 24-Week DBPC Period				Part B: 24-Week OLE Period					Unscheduled Visit	Early Discontinuations
Study Visit	S-1	S-2	1	2	3	4	5	6	7	8	9		
Study Week	-8	-6	0	2	8	16	24	28	32	40	48		
Window, ±Day(s)		5											
ENROLMENT PROCEDURE													
Informed Consent	X												
Inclusion / Exclusion Criteria	X	X											
E1 Escorial Criteria	X												
Randomization		X											
MEDICAL PROCEDURE													
Bone Marrow Aspiration		X											
Neurological Examination	X		X	X	X	X	X	X	X	X	X	X	X
Chest X-ray or Chest CT Scan	X												
TREATMENT PROCEDURE													
IT Injection of NurOwn			X		X	X	X		X	X			
Prior & Concomitant Medications	X	X	X	X	X	X	X	X	X	X	X	X	X
DISEASE ACTIVITY													
ALSFRS-R	X		X	X	X	X	X	X	X	X	X	X	X
SAFETY LABS													
Chemistry, Hematology…	X		X	X	X	X	X	X	X	X	X	X	X

Eligibility Criteria

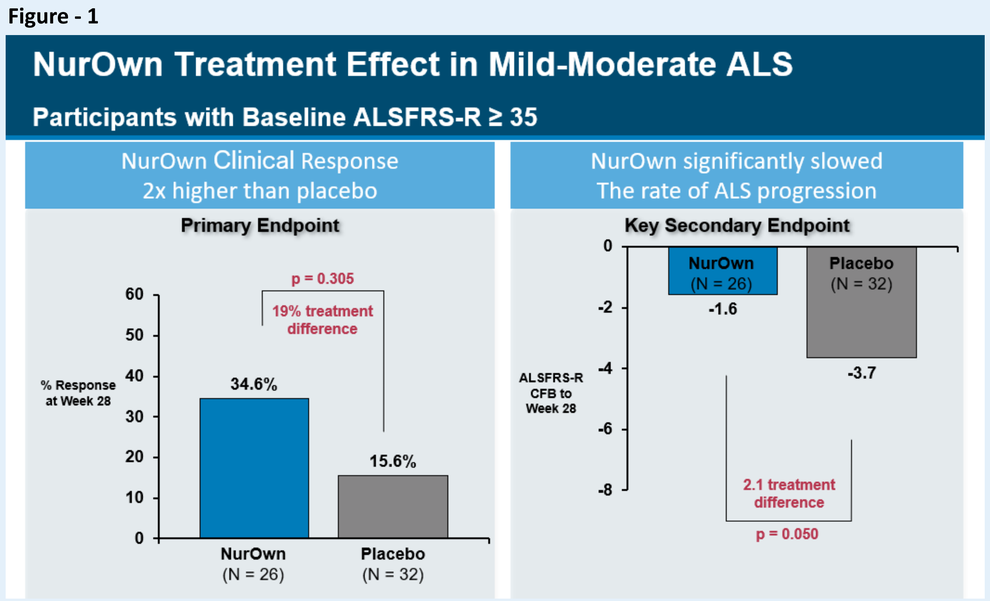
Up to approximately 200 participants with early and mild-moderate ALS will be allowed to enter Part-A to receive either NurOwn® or Placebo, while being allowed to also receive concomitant treatment of an approved standard of care (e.g., riluzole, edaravone, sodium phenylbutyrate/taurursodiol).

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
- Having onset of ALS symptoms within the prior 24 months
- Upright Slow Vital Capacity (SVC) ≥65% of predicted for gender, height, and age
- Participants must adhere to restrictions regarding pregnancy, contraception, and lactation
- 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

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

Indication	Preclinical	Phase 1	Phase 2	Phase 3	Milestones
NurOwn® MSC-NTF Cells Platform					
ALS				Phase 3	Published in Muscle & Nerve - 2021*
				Phase 3b	FDA Feedback: SPA being requested
Progressive MS					Published in MS Journal - 2022**
Parkinson's Disease					
MSC-NTF Exosomes Platform					
ARDS					

Contact Information

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