

# CSF biomarker correlations with primary outcome in NurOwn Phase 3 clinical trial

Merit Cudkowicz<sup>1</sup>, Robert Brown<sup>2</sup>, Revital Aricha<sup>3</sup>, Stacy Lindborg<sup>3</sup>, Anthony Windebank<sup>4</sup>, Nathan Staff<sup>4</sup>, Namita Goyal<sup>5</sup>, James Berry<sup>1</sup>, Robert Miller<sup>6</sup>, Jonathan Katz<sup>6</sup>, Matthew Burford<sup>7</sup>, Yossef S. Levy<sup>3</sup>, Chaim Lebovits<sup>3</sup>, Yael Gothelf<sup>3</sup>, Bruno Boulanger<sup>8</sup>, Munish Mehra<sup>9</sup>, Ralph Kern<sup>3</sup>

1. Massachusetts General Hospital, Boston, MA, USA 2. UMass Medical School, Worcester, MA, USA 3. BrainStorm Cell Therapeutics, NYC, NY, USA 4. Mayo Clinic, Rochester, MN, USA 5. UCI, Irvine CA, USA 6. CPMC, SF, CA, USA 7. Cedars Sinai, Los Angeles, CA, USA 8. Pharmalex, Brussels, Belgium 9. Tigermid, Sommerset NJ, USA



## Background

MSC-NTF cells (NurOwn<sup>®</sup>) are autologous bone-marrow derived mesenchymal stem cells (MSC) induced to secrete high levels of neurotrophic factors (NTFs). MSC-NTF cells were administered in three bimonthly intrathecal injections to ALS participants in a US Phase 3 multicenter double-blind placebo-controlled trial to evaluate safety and efficacy (NCT03280056).

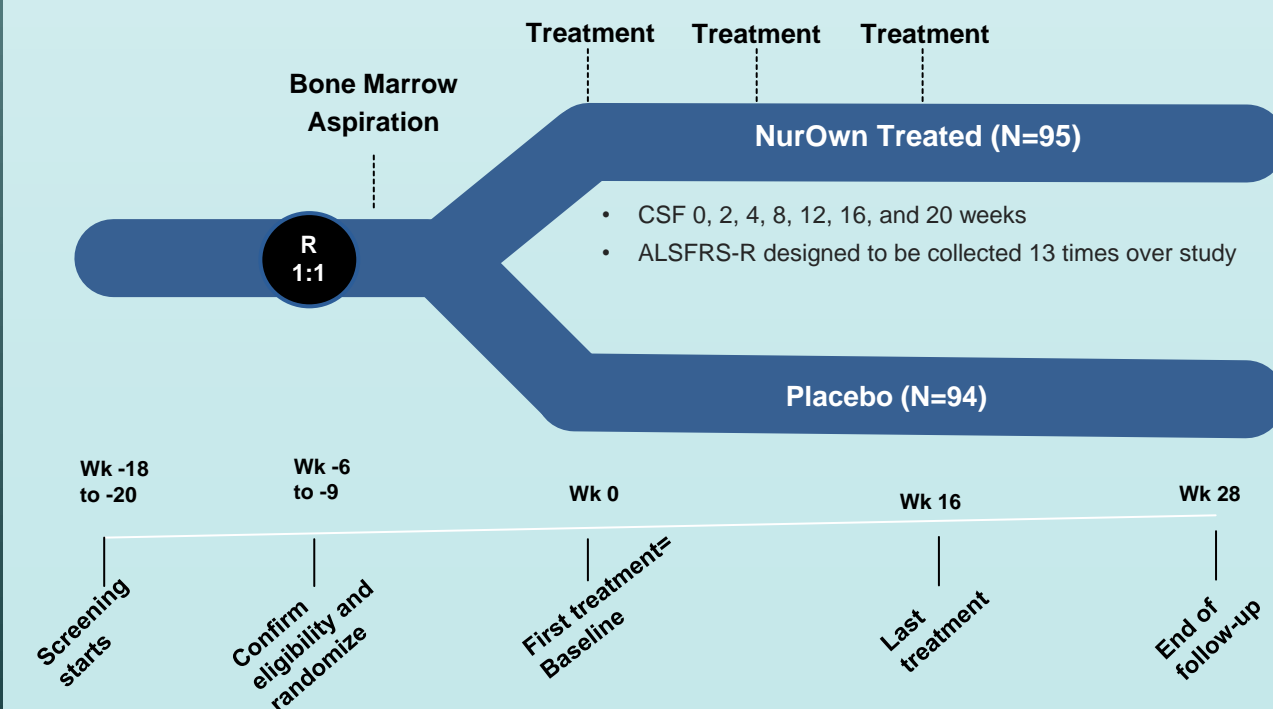
## Objective

To relate CSF biomarkers with primary ALSFRS-R outcome in the Phase 3 placebo-controlled trial.

## Design/Methods

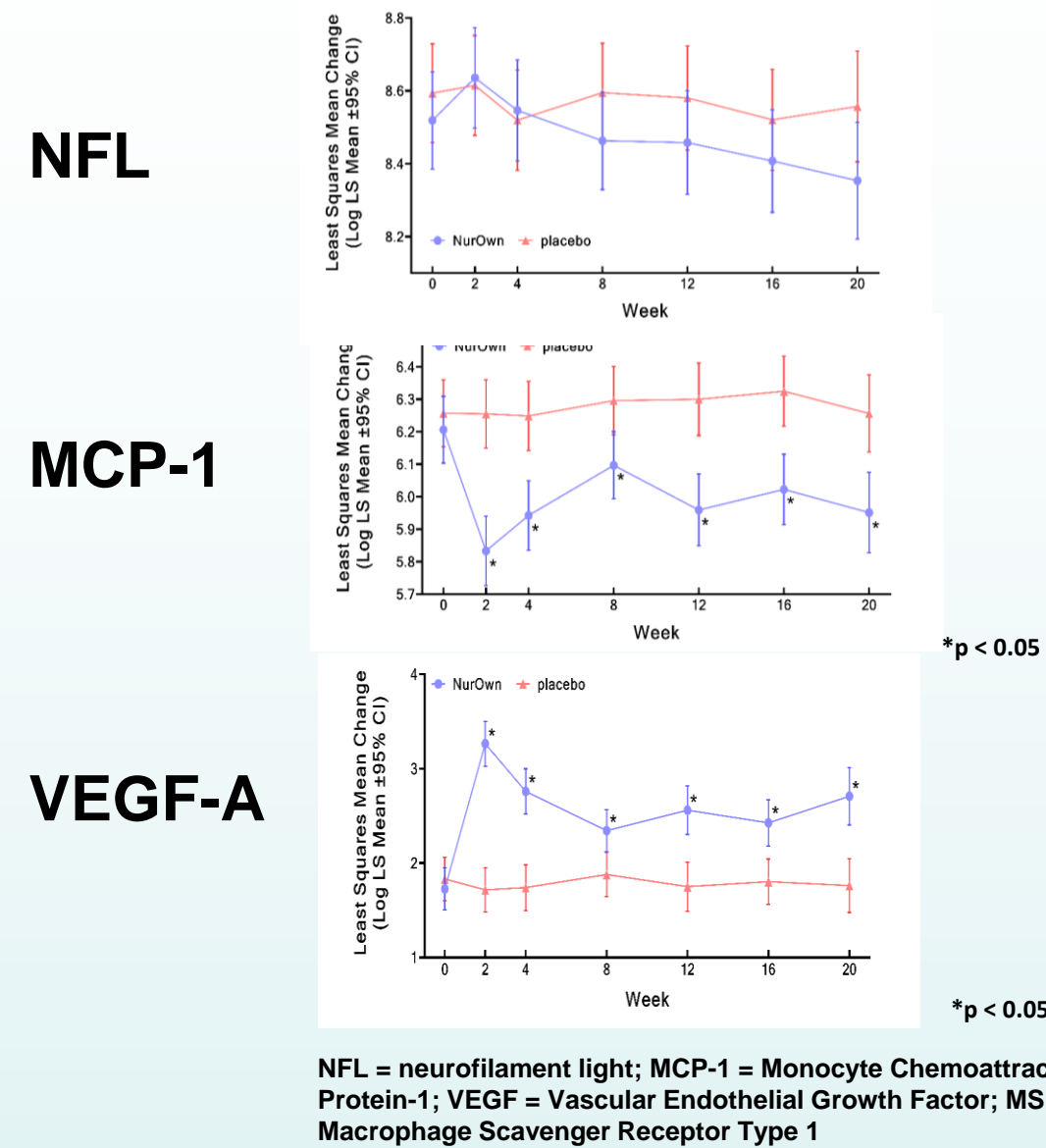
The primary endpoint was a responder analysis of the change in rate of ALSFRS-R decline, defined by an improvement of  $\geq 1.25$  points/month compared to the pre-treatment ALSFRS-R slope. CSF was collected at 7 time points, at baseline (before treatment) and through week 20. CSF biomarker selection (n=37) and biomarker statistical analyses were prespecified in a statistical analysis plan that was completed prior to unblinding. An unbiased stepwise logistic regression analysis was performed using log values (biomarker values and changes, and ENCALs model\*) to identify the minimum set of CSF biomarkers in addition to ENCALs (independent variables) that predicted the primary clinical outcome (dependent variable).

## Study Schematic



## Results

CSF Neurodegenerative (NFL), Neuroinflammatory (MCP-1), and Neuroprotective (VEGF) biomarker changes over time (LSMean, 95% CI).



## Stepwise linear regression model:

Predictive Biomarkers Show 82.5% Accuracy in ROC Analysis (NurOwn and Placebo Treatment Arms)

Stepwise logistic model	Baseline value	Post baseline
ENCALS Model*	✓	✓
MCP-1		✓, $\Delta$
NFL	✓	✓
Fetuin A		✓, $\Delta$
VEGF-A		✓
S100B	✓	
MSR1		✓

Legend:   
■ Neurodegeneration   
■ Neuroinflammation   
■ Neuroprotection

Legend:   
 ✓ : biomarker values   
 $\Delta$  : change in biomarker

\* Reflective of overall baseline health of participants. ENCALs Model uses terms: Age of onset, FVC, Duration from onset of symptoms to first treatment, Bulbar onset, ALSFRS-R slope, 'Definite' ALS

## Discussion

- ALS is a complex disease in which neurodegeneration, neuroinflammation and failure of intrinsic neuroprotective mechanisms may play an important role<sup>1</sup>
- NurOwn treatment resulted in consistent changes in CSF neurodegenerative (NFL), neuroinflammatory (MCP-1), and neuroprotection (VEGF-A) biomarkers, while placebo levels remained stable.
- A detailed analysis of CSF biomarkers in this phase 3 trial suggests that the primary clinical responder outcome may be predicted by a combination of neurodegenerative, neuroinflammatory and neuroprotection biomarkers.
- Statistical Modeling highlights biomarkers that are predictive of NurOwn treatment response with good accuracy (82.5%)

## Conclusions

- Predictive CSF biomarkers identified in the stepwise logistic regression analysis will be an important step in furthering our understanding of the mechanism of action of NurOwn in ALS as well as in future studies that use CSF biomarkers to advance ALS science.

1. Brown, Al-Chalabi NEJM 2017