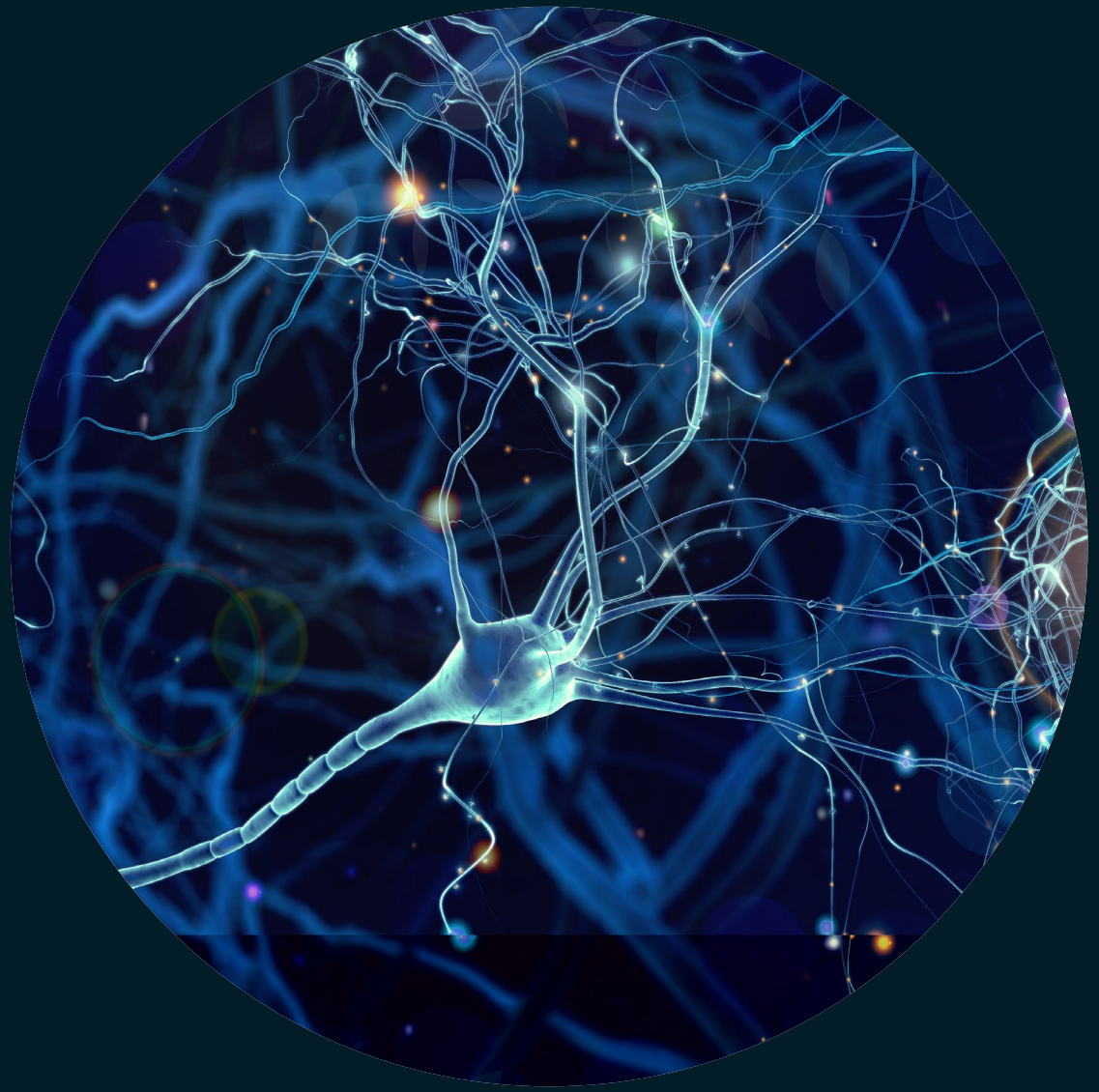

# NurOwn Targets Multiple Disease Pathways in ALS Phase 3 Trial: A Biomarker Analysis

Brown R, Aricha R, Boulanger B, Windebank A, Goyal N, Miller R, Burford M, Berry J, Katz J, Staff N, Kaspi H, Abramov N, Mehra M, Kern R, Lindborg S, Gothelf Y, Lebovits C, Cudkowicz M

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# Disclosures

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**Also supported by grants from the California Institute for Regenerate Medicine, the ALS Association and I AM ALS**

**Robert Brown**: Consults for APIC Bio and serves on advisory boards of ALSOne, Angel Fund for ALS Research, the Healey Center, ALS Finding a Cure, Project ALS, and NEALS

**Merit Cudkowicz:** Received personal compensation consulting for Lilly Avexis, Pontifax, Orion, MT Pharma, Denali, Biogen, Pharmnext, Treeway, Revalasio, Takeda, Aclipse, Biohaven, Sunovian, Anelixis, Disarm, ALS Biopharma, Cytokinetics, RRD, Immunity Pharma, Helixsmith, Wave, Transposon, Quralis, Faze, Regeneron, and AB Sciences

**Namita Goyal:** received research support from Alexion, Brainstorm Cell Therapeutics, Cytokinetics, Fulcrum, Healey Platform, Kezar, Medicinova, Octapharma, Orion, Orphazyme; served on Advisory Boards for Acceleron, Alexion, Argenx, CSL Behring, MT Pharma, Sanofi Genzyme, Sarepta, UCB; received travel reimbursement and honoraria; and served on the speaker's bureau for CSL

**James Berry:** reports personal fees from Biogen, Clene Nanomedicine, MT Pharma of America, MT Pharma Holdings of America, Janssen; grants from Alexion, Biogen, Amylyx Therapeutics, MT Pharma of America, Anelixis Therapeutics, Genentech, Rapa Therapeutics, MT Pharma Holdings of America, nQ Medical, NINDS, Muscular Dystrophy Association, ALS One, ALS Association, ALS Finding A Cure, Rapa Therapeutics; and has equity in ReactNeuro

**Nathan Staff:** reports research support from the National Institutes of Health (R01 CA21887), Regenerative Medicine Minnesota, Target ALS, and ALS Association

**Jonathan Katz:** reports consulting fees from MT Pharma, Denali Therapeutics, Biogen, Genetech, Amylyx, Cytokinetics, Wave, and Calico

**Anthony Windebank, Robert Miller, Matthew Burford:** have no conflicts of interest to report

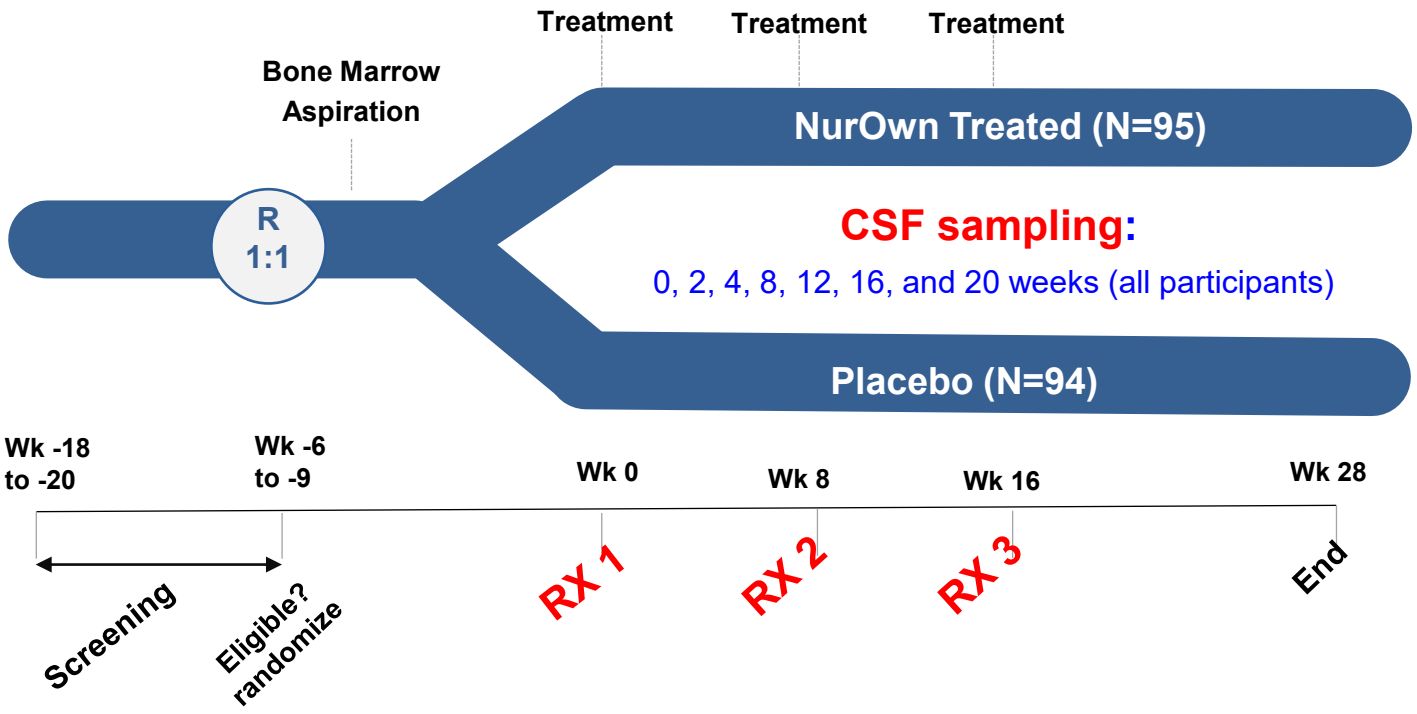
**Revital Aricha, Haggai Kaspi, Natalie Abramov, Ralph Kern, Yael Gothelf, Chaim Lebovits, Stacy Lindborg:** are employed by Brainstorm Cell Therapeutics

**Bruno Boulanger** is employed by PharmaLex

**Munish Mehra** is employed by Tigermed

# Phase 3 Trial of NurOwn® in ALS Patients : Protocol

## Double-blind, Placebo-controlled, Randomized Trial




**Inclusion criteria:**

- ALSFRS-R ≥ 25 at Screening
- Upright SVC ≥ 65% of predicted for gender, height, and age at Screening
- Onset of ALS disease symptoms within 24 months of Screening
- Decline in ALSFRS-R total score of 3 or more points in the 12 weeks before randomization.
- ALS diagnosed by revised El Escorial criteria as possible, laboratory-supported probable, probable, or definite

**The primary and secondary endpoints failed to reach statistical significance in the overall study population**

**Pre-specified and post-hoc analyses suggest a potential treatment effect with MSC-NTF across the primary and secondary efficacy**

# Three Pathways Interrogated by Biomarkers

- Neurodegeneration (5)

  NfL, UCH-L1, pNfH, DR6, Fetuin-A

- Neuroprotection (7)

  Follistatin, VEGF, Clusterin, BDNF, OPG, GDF-15, LIF

- Neuroinflammation (9)

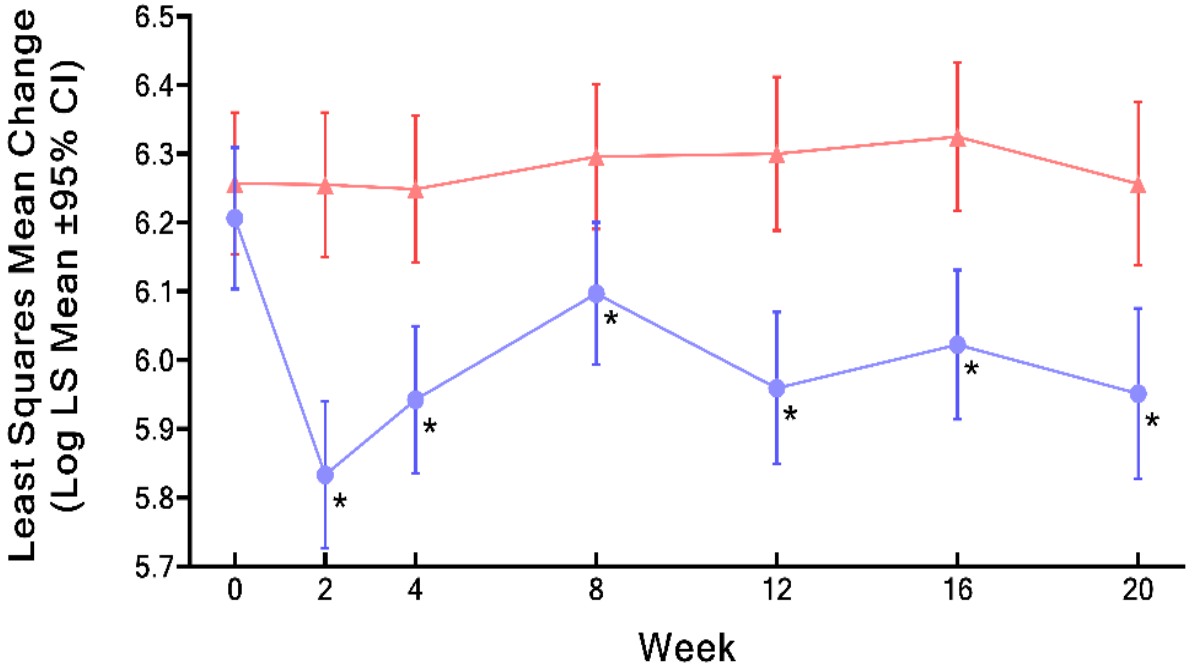
  CHI3L1, Chit-1, IP-10, MCP-1, Trem-2, SDF1a, S100B, MSR1, NMNAT1

# Three Approaches to Mapping Biomarkers onto Disease Pathways

- Analysis of Individual Biomarkers
- Principle component analysis of all biomarkers simultaneously within each pathway
- Regression modeling using all biomarkers to predict outcome

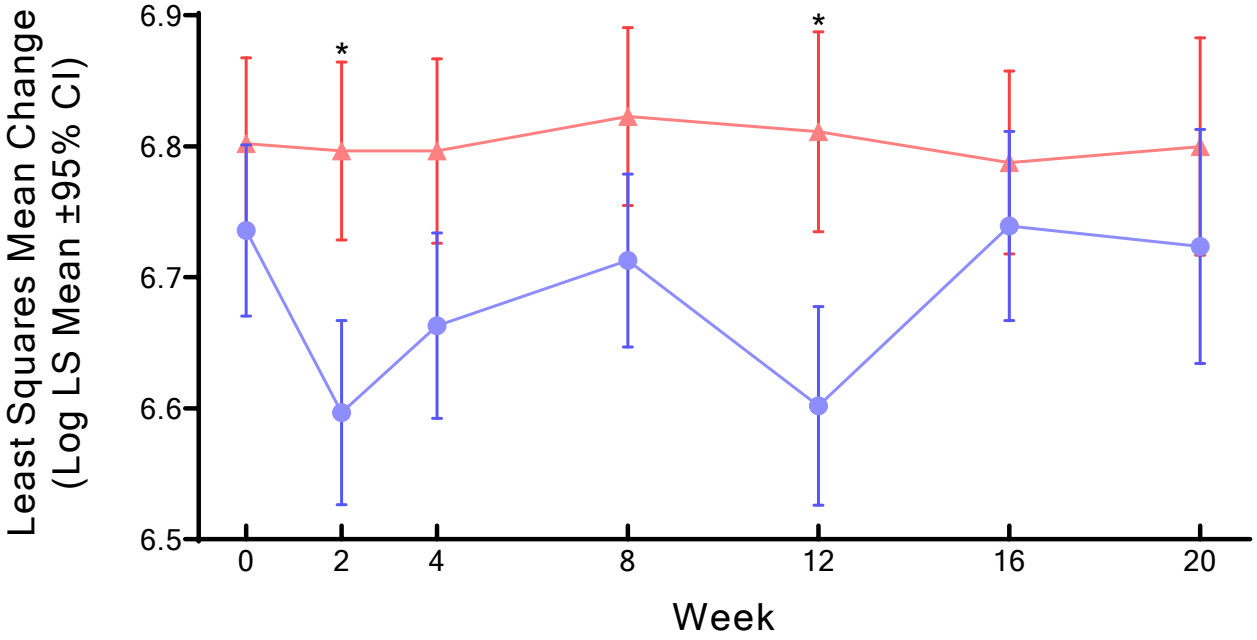
# NurOwn significantly lowers pro-inflammatory biomarkers over time compared to placebo

**MCP-1: Statistically significant reduction with NurOwn at each visit, and significant overall treatment effect**




Monocyte chemoattractant protein 1

**SDF-1a: Statistically significant reduction with NurOwn, significant overall treatment effect**




Stromal cell derived factor 1a

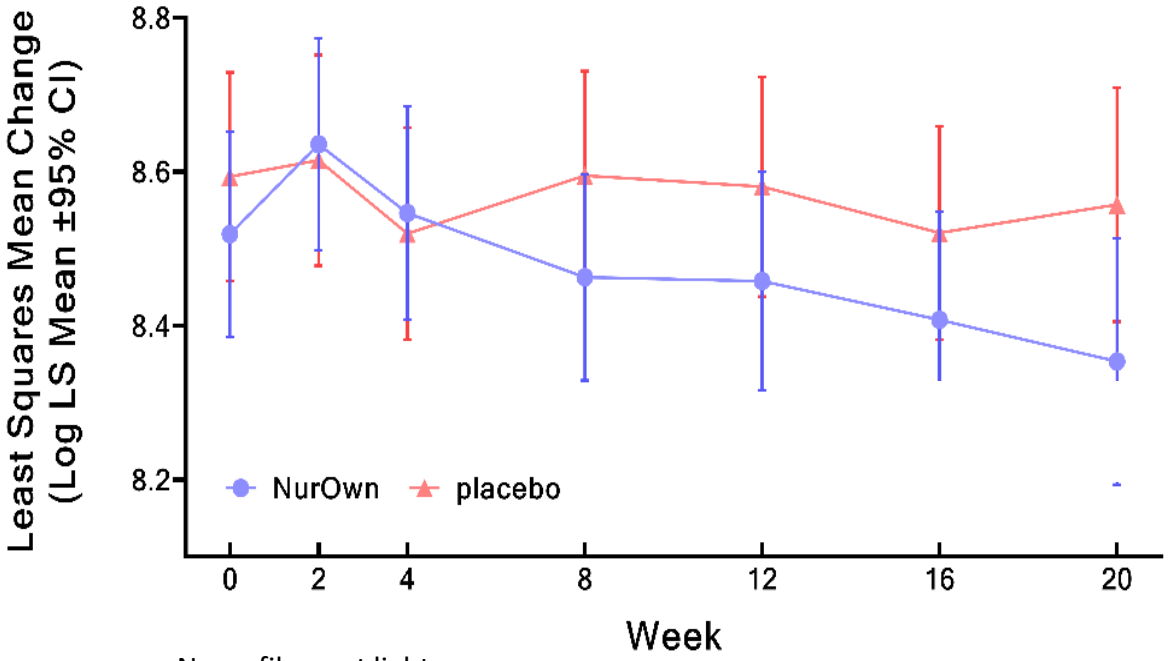
NurOwn placebo

*p < 0.05

**MCP-1 and SDF-1a:**
Treatment effect p < .01
Visit effect p< .01

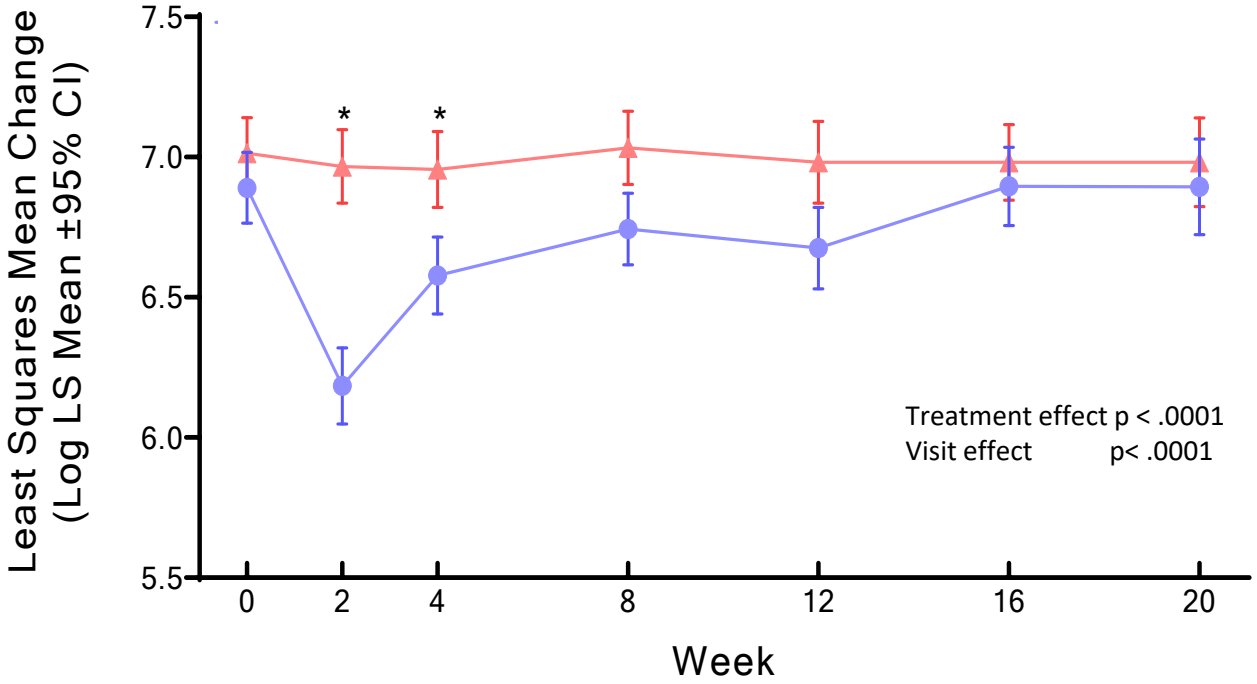
# NurOwn lowers some biomarkers of neurodegeneration over time compared to placebo

**NfL: NurOwn values lowered 82% compared to Placebo at week 20**




Neurofilament light

**DR6: Statistically significant reduction with NurOwn, significant overall treatment effect**




Death receptor 6

NurOwn placebo

*p < 0.05

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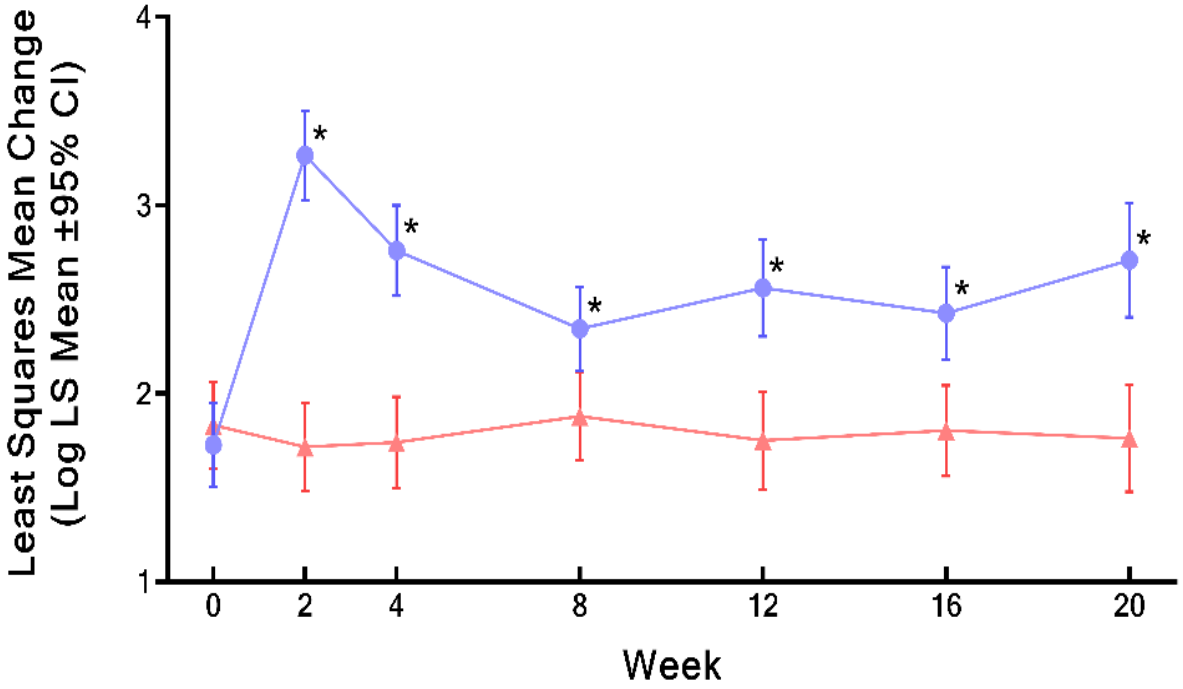
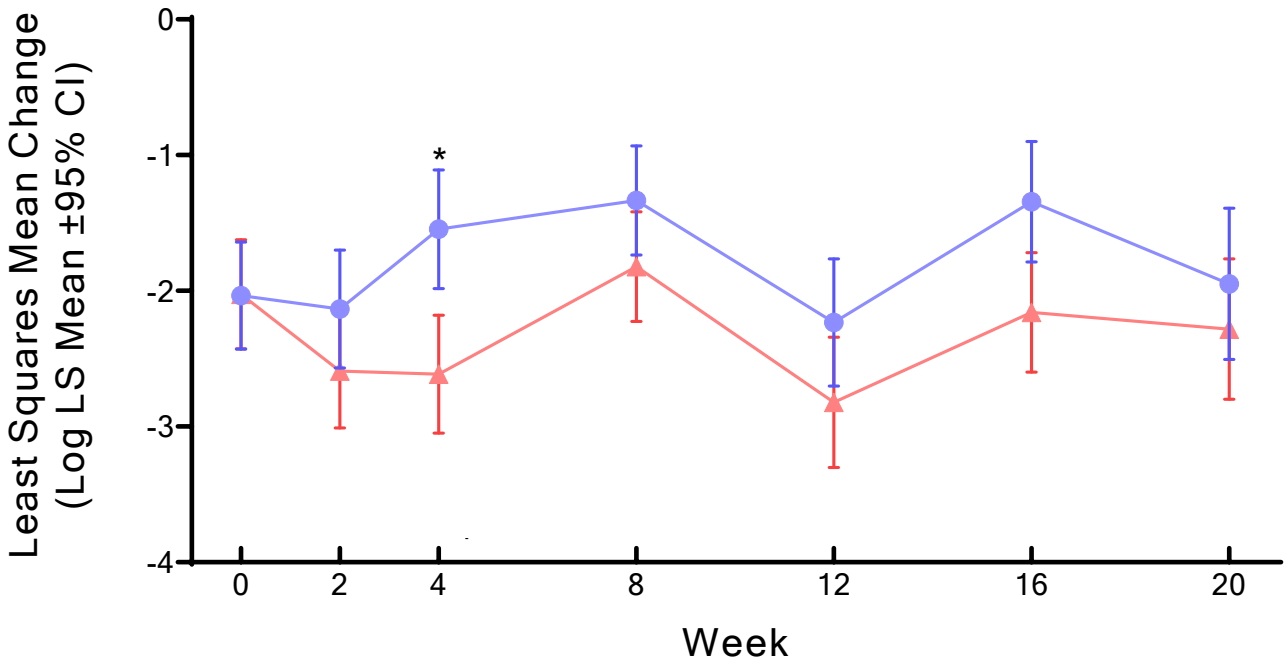
# NurOwn significantly elevates neuroprotective biomarkers over time compared to placebo

**VEGF: Statistically significant increase with NurOwn at each visit, and significant overall treatment effect (2-fold increase)**




Vascular endothelial growth factor

**BDNF: Statistically significant increase with NurOwn, with overall significant treatment effect**




Brain derived neurotrophic factor

NurOwn placebo

*p < 0.05 **VEGF and BDNF:**
Treatment effect p < .001
Visit effect p < .001

# Three Approaches to Mapping Biomarkers onto Disease Pathways

- Analysis of Individual Biomarkers
- Principle component analysis of all biomarkers simultaneously within each pathway
- Regression modeling using all biomarkers to predict outcome

# Statistical Analysis of Biomarker data through Principal Components

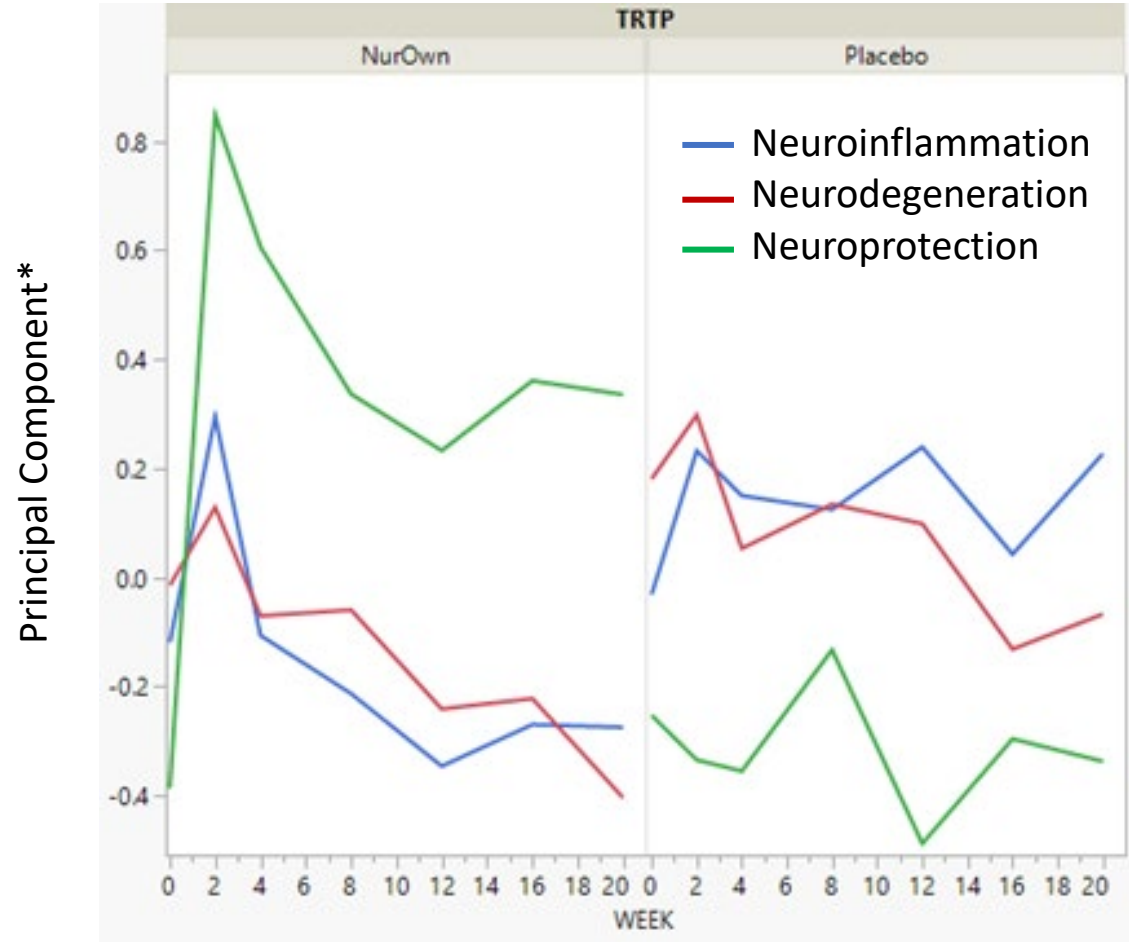
**NurOwn therapy reduces markers of Neuroinflammation and Neurodegeneration, and increases Neuroprotection**

**Trend with individual biomarkers confirmed across biomarkers with PCA**

- **Neuroinflammation decreased with NurOwn** treatment over 20 weeks
  - Placebo Neuroinflammation levels remain high
- **Neurodegeneration decreased with NurOwn**
  - Placebo Neurodegeneration levels decrease across the study, remain elevated relative to NurOwn.
- **Neuroprotection increased with NurOwn** treatment and is maintained over 20 weeks
  - Placebo Neuroprotective levels remain low

Biomarkers driving PCA results:

- Neuroinflammation (5/9): CHI3L1, Chit-1, IP-10, MCP-1, Trem2
- Neurodegeneration (3/4): NfL, UCH-L1, pNfH
- Neuroprotection (4/7): Follistatin, VEGF, Clusterin, BDNF




**Graph produced the first Principal component from each pathway*

# Three Approaches to Mapping Biomarkers onto Disease Pathways

- Analysis of Individual Biomarkers
- Principle component analysis of all biomarkers simultaneously within each pathway
- Regression modeling using all biomarkers to predict outcome
  (Stepwise forward regression model – machine learning algorithm)

# Final Model identifies Biomarkers predictive of Primary Endpoint with high accuracy

**Leveraging model with biomarkers, treatment effect on Primary Endpoint is statistically significant (p=0.003)**

| Stepwise logistic model | Post baseline |
|---|---|
| ENCALS Model* | ✓ |
| MCP-1 | ✓, Δ |
| NfL | ✓ |
| Fetuin A | ✓, Δ |
| VEGF | ✓ |
| MSR1 | ✓ |

Neuroinflammation
Neurodegeneration
Neuroprotection

✓ biomarker
Δ change in biomarker

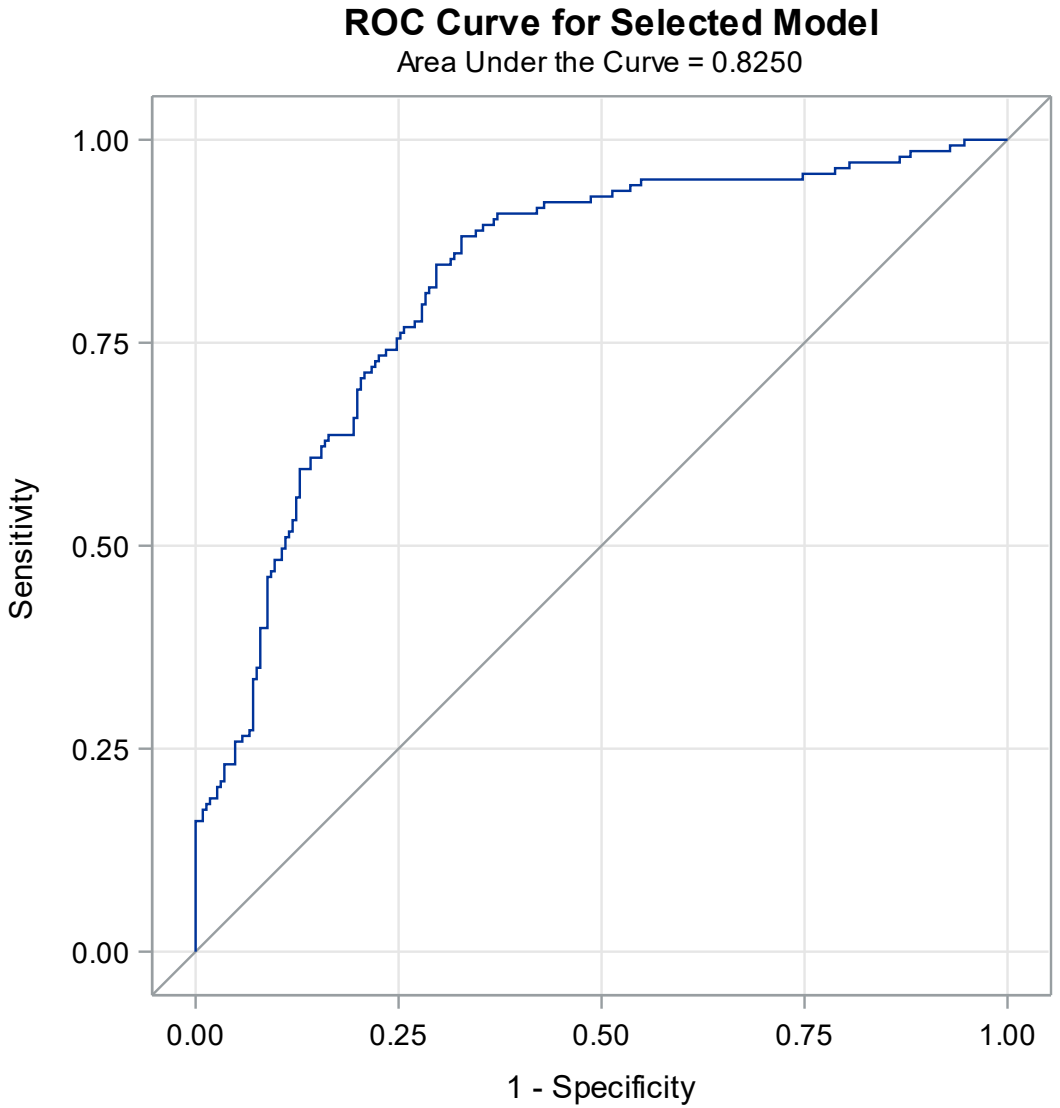
- **Baseline health was important to predicting clinical response**
  - ENCALS model term
- **Biomarker data was important to the prediction of clinical response**
  - Markers of neuroinflammation, neurodegeneration and neuroprotection were all in the final model
  - Highlights the importance of all 3 pathways
- **Information about the magnitude of change for MCP-1 and Fetuin-A contributed to the accuracy of the model prediction**
  - larger change in MCP-1 more likely to respond
  - larger change in Fetuin-A more likely to respond

* ENCALS model Reflective of overall baseline health of participants.

Model uses terms: Age of onset, FVC, Duration from onset of symptoms to first treatment, Bulbar onset, ALSFRS-R slope, 'Definite' ALS

# NurOwn response: Stepwise linear regression model to select predictive biomarkers

## 82.5% accuracy of model predicting clinical response




Receiver Operating Curve

- Measures accuracy of the model
- Area Under the Curve (AUC)
- Values range from 0-100%
  - 50% is equivalent to a random guess
  - >80% represents high classification accuracy

# Conclusions

- NurOwn significantly and consistently elevates markers of neuroprotection, and significantly lowers markers of neuroinflammation and neurodegeneration over time compared to placebo
  - The same conclusion is drawn from individual markers and summaries of markers using PCA
- Prespecified statistical modeling leveraging machine learning highlights biomarkers that are predictive of treatment response with NurOwn with high accuracy (>80%)
  - Markers of neuroinflammation, neurodegeneration and neuroprotection were all selected in the final model
- These results enhance our understanding of NurOwn's mechanism of action in ALS
- NurOwn cell therapy targets multiple disease pathways and provides additional evidence linking the mechanism of action to NurOwn's impact on ALS progression (primary endpoint).

# Manufacturing Sites



City of Hope

**City of Hope Center for Biomedicine & Genetics**

DANA-FARBER CANCER INSTITUTE

**Dana-Farber Harvard Cancer Center**

***Cell Manipulation Core***

# Treatment Centers

University of Massachusetts Medical School

MASSACHUSETTS GENERAL HOSPITAL

MAYO CLINIC

UCIRVINE

CEDARS-SINAI

Sutter Health
Sutter Pacific Medical Foundation

# Funding

CIRM
CALIFORNIA'S STEM CELL AGENCY

ALS ASSOCIATION

I AM ALS

# Thank You !!

# Extra slides

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# Biomarkers with significant explanatory value for Clinical Response, NurOwn and Placebo

| | NurOwn Phase 3 | | Description | Published relationships |
|---|---|---|---|---|
| | **Baseline value** | **Post baseline** | **Mechanism of Action** | **CSF levels correlate with ALS survival** |
| ENCALS Model* | ✓ | ✓ | -- | ✓ |
| MCP-1 | | ✓, Δ | B-chemokine Neuroinflammation | ✓ |
| NfL | ✓ | ✓ | Specific marker of neuronal injury, possible biomarker of neurological disease activity | ✓ |
| Fetuin-A | | ✓, Δ | Inhibits proinflammatory mediator pathways | |
| S100b | ✓ | | Astrocyte inflammatory mediator, RAGE activation | ✓ |
| VEGF | | ✓ | Neuroprotection Growth factor | |
| MSR1 | | ✓ | Anti-inflammatory, Macrophage scavenger receptor DAMP clearance | |

Neuroinflammation, Neurodegeneration, Neuroprotection

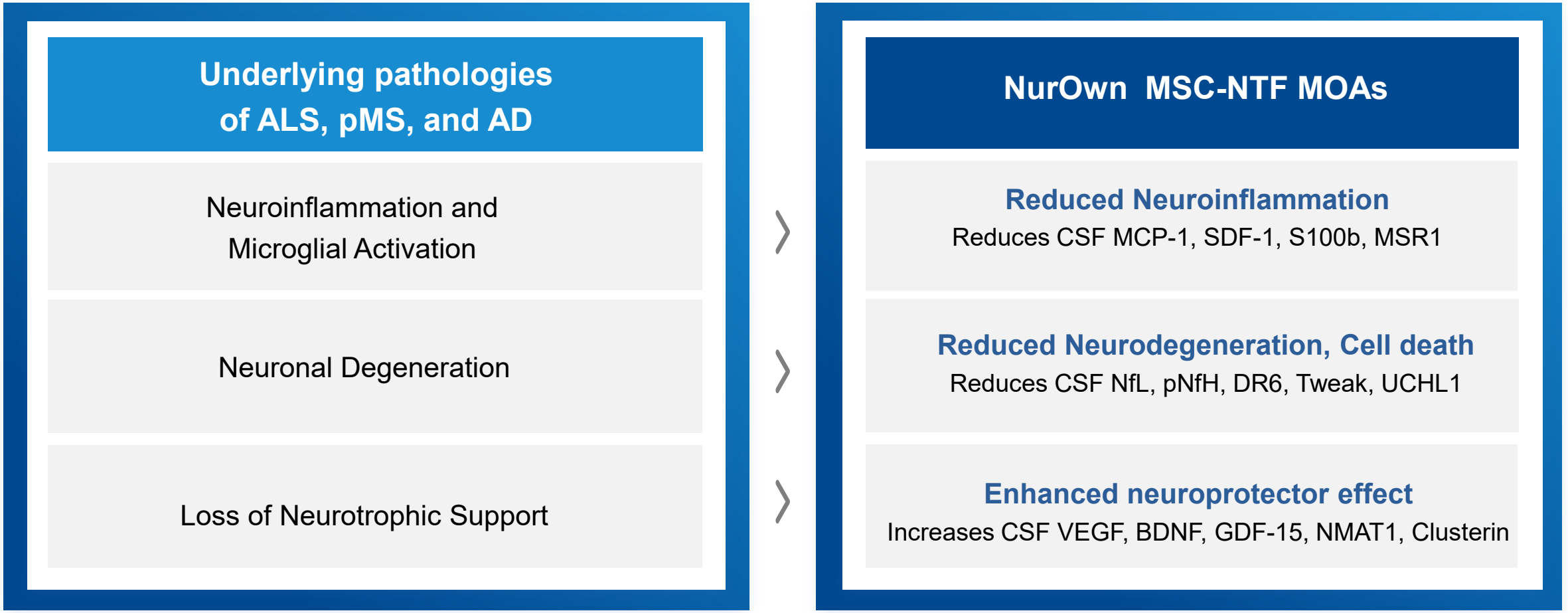
* Reflective of overall baseline health of participants.

Model uses terms: Age of onset, FVC, Duration from onset of symptoms to first treatment, Bulbar onset, ALSFRS-R slope, 'Definite' ALS

✓ : biomarker values
Δ : change in biomarker

# NurOwn MOA: Lessons learned from Phase 2, Replicated in Phase 3

## Neuroinflammation, Neurodegeneration, and Neuroprotection Biomarkers




ALS: Amyotrophic lateral sclerosis; pMS: Progressive multiple sclerosis; AD: Alzheimer's Disease; MOAs: Mechanisms of action