The Debamestrocel (NurOwn) Treatment Effect in Phase 3 as accessed by ALSFRS-R and CSF Biomarkers

13TH ANNUAL CALIFORNIA ALS RESEARCH SUMMIT

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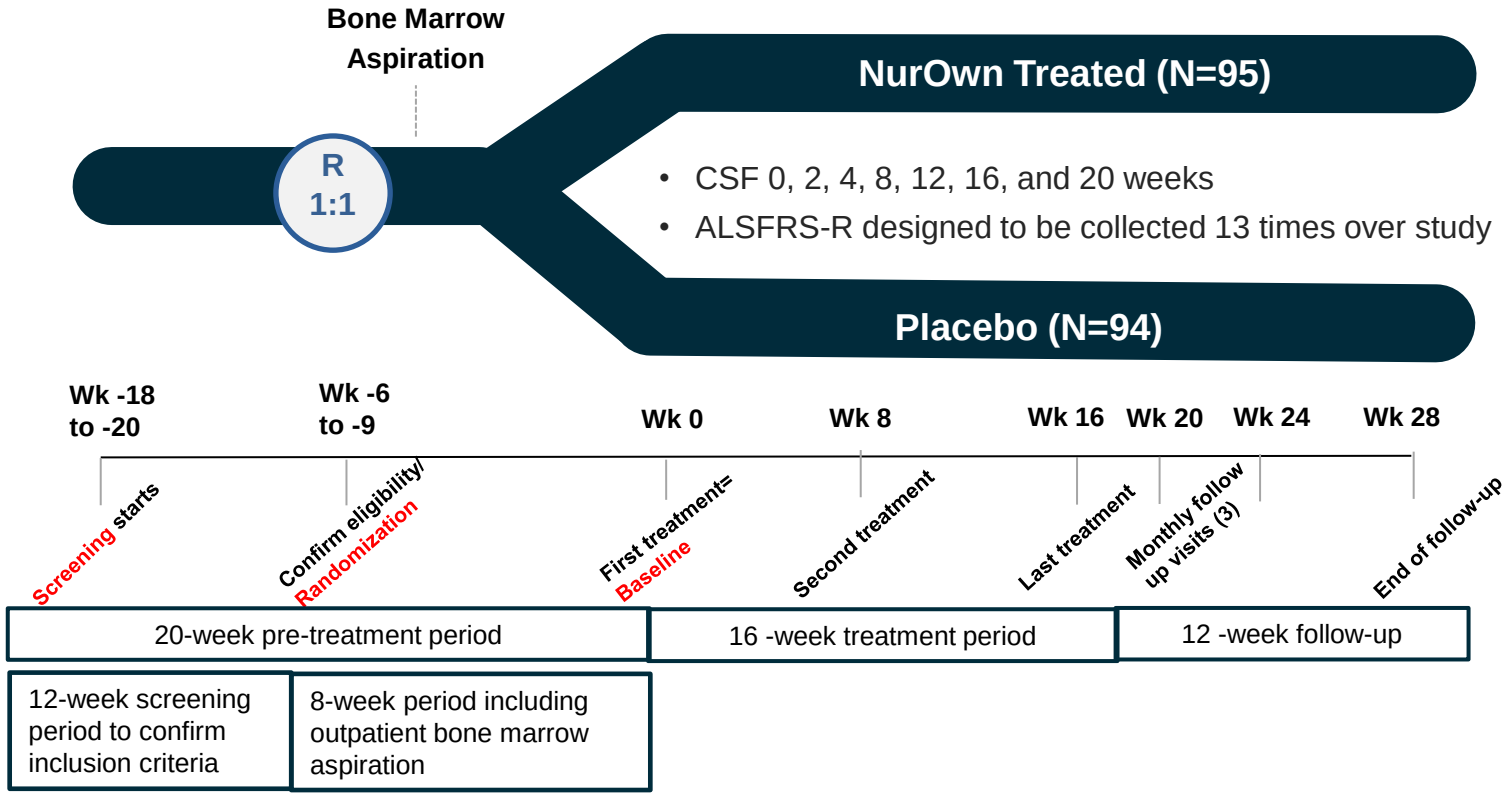
Phase 3 Trial Study Design: Designed to exclude slow progressors

Double-blind, Placebo-controlled, Randomized Trial



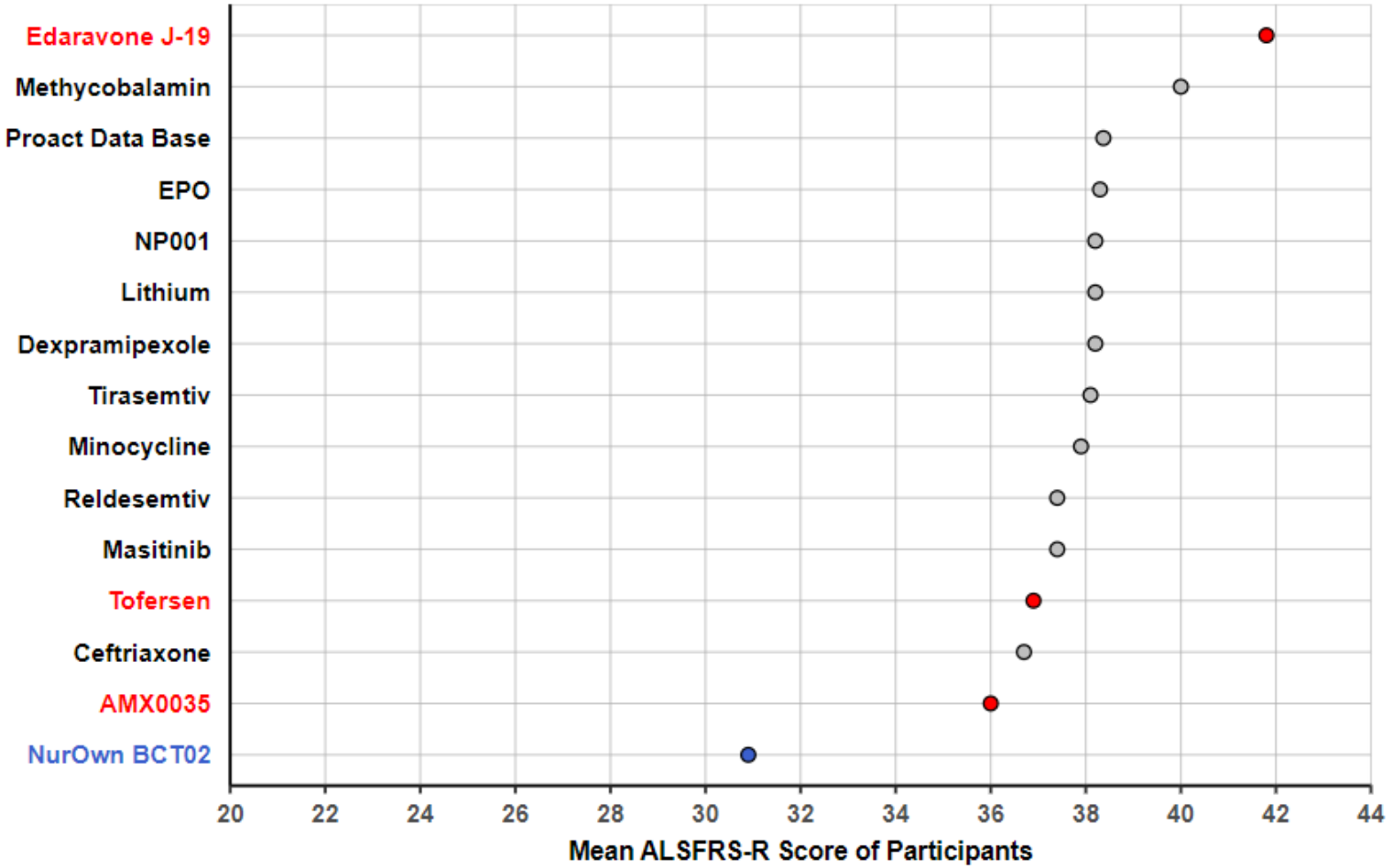
Designed to exclude slow progressors.

Inclusion criteria specified:

- ALSFRS-R ≥ 25 at Screening Visit (Not at Baseline).
- Decline in ALSFRS-R total score of 3 or more points in the 12 weeks before randomization.

Cudkowicz, M, Lindborg S, Goyal N, et al. Musc Nerve, 2022

NurOwn Phase 3 Featured Participants with Advanced ALS Disease Resulting in Floor Effect



Per FDA: "[a] floor effect can occur at the item level or at the scale score level. *The floor effect occurs when the scale of measurement is not able to capture progression at the bottom of the scale*."

FDA, Patient-Focused Drug Development Guidance Public Workshop, Methods to Identify What is Important to Patients & Select, Develop, or Modify Fit-for-Purpose Clinical Outcomes Assessments at 9 (Oct. 15-16, 2018)

Participants with Baseline ALSFRS-R ≤ 25 Impacted by ALSFRS-R Floor

- 23% (44/189) of participants with baseline ALSFRS-R ≤ 25
- ALSFRS-R cannot measure further decline once items reach 0
- Impacts ability to differentiate rates of clinical decline between treatment groups

ALSFRS-R Subscale	% Participants with Value of 0 at Baseline
Bulbar	7%
Fine Motor	42%
Gross Motor	37%
Respiratory	1%

70% of decline occurs in FM and GM subdomains

Inability to Measure Further Decline Results in Misclassification of Response on Primary Endpoint

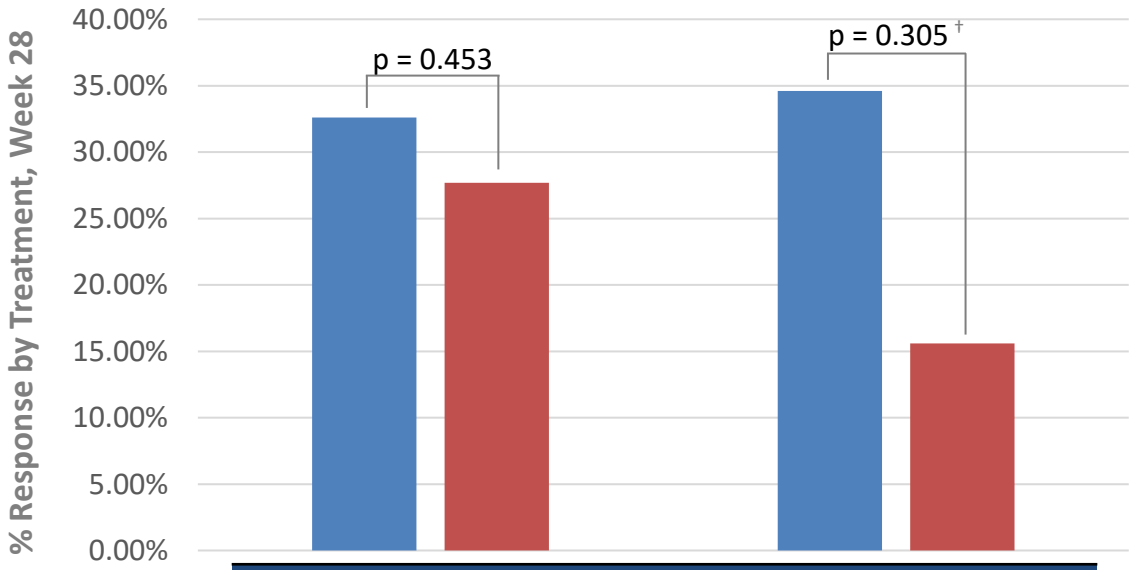
- **Participants can achieve response criteria (i.e., ≥ 1.25 points/month reduction in decline compared to pre-treatment period) because of floor effect of scale**
  - **Suggesting that participants with worst scores had a clinical response**

- **Floor effect must be addressed to draw valid treatment conclusions from the data**

- **Possible to draw legitimate conclusions from BCT-002**
  - **Pre-specified subgroup and endpoints to estimate treatment effect in study**
  - **Pre-specified threshold-based analysis minimizes floor effect in the analysis, by the nature of the threshold being removed from the bottom of the scale**

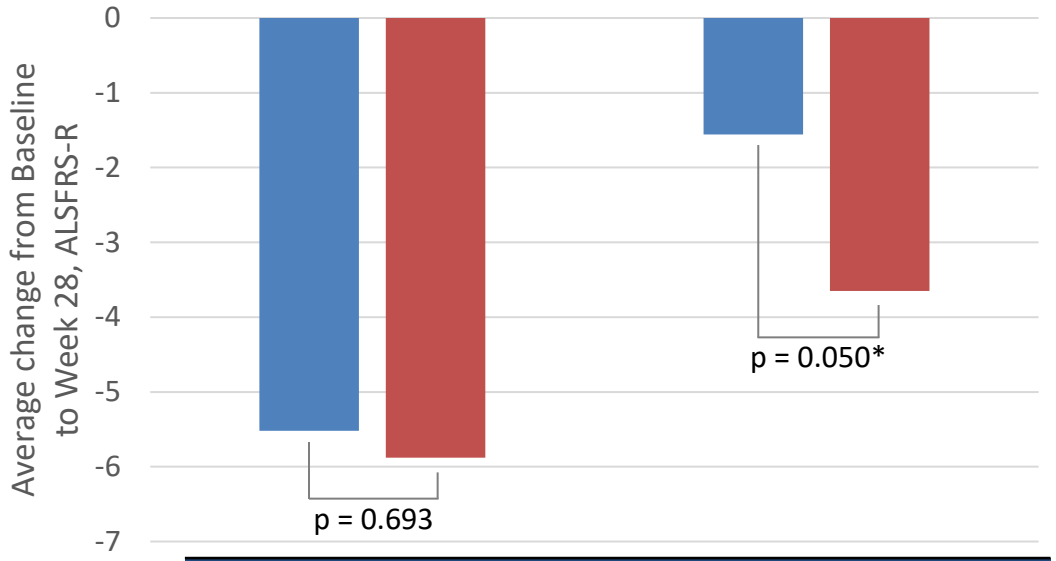
NurOwn treatment suggests effect in participants with less advanced disease

Primary Endpoint: % Response at week 28



	All Participants (N=189)	ALSFRS-R ≥ 35 (n=58)
NurOwn	32.60%	34.60%
Placebo	27.70%	15.60%
Difference	4.9%	19%

Secondary Endpoint: Average Change from baseline to Week 28, ALSFRS-R



	All Participants (N=189)	ALSFRS-R ≥ 35 (n=58)
NurOwn	-5.52	-1.56
Placebo	-5.88	-3.65
Difference	0.36	2.09

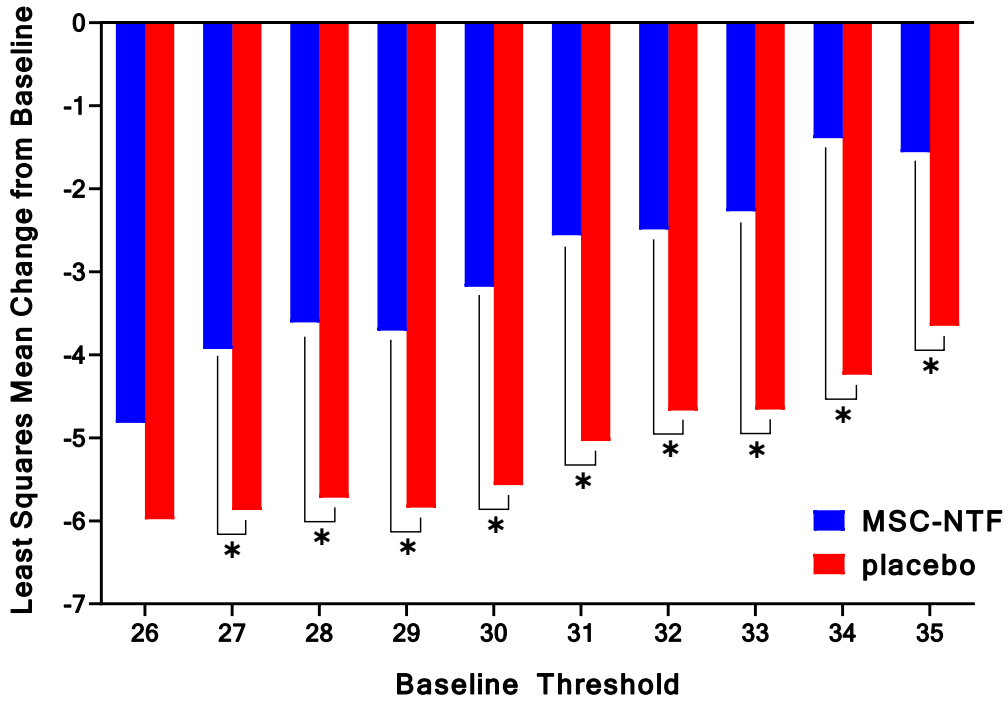
*p ≤ 0.05, nominal p-value

†Evidence on the primary endpoint aligns with historical data and power calculations (35% NurOwn vs. 15% placebo response)

Cudkowicz, M, Lindborg S, Goyal N, et al. Musc Nerve, Jan 2022
Supplemental File & Erratum published Aug 2022

ALS Phase 3 Secondary Endpoint by Baseline ALSFRS-R > 25: NurOwn participants with less advanced disease had greater preservation of function compared to Placebo

ALSFRS-R MMRM Change from Baseline to Week 28 Secondary Endpoint					
ALSFRS-R Baseline Score	**n (%) total participants**	**MSC-NTF LS mean (SE)**	**Placebo LS mean (SE)**	**Delta**	**p-value**
≥ 35	48 (25)	-1.56 (0.82)	-3.65 (0.70)	2.09	0.050*
≥ 34	57 (30)	-1.39 (0.96)	-4.24 (0.80)	2.86	0.022*
≥ 33	69 (37)	-2.27 (0.90)	-4.66 (0.79)	2.39	0.044*
≥ 32	78 (41)	-2.49 (0.78)	-4.67 (0.74)	2.18	0.040*
≥ 31	80 (42)	-2.56 (0.78)	-5.04 (0.75)	2.48	0.020*
≥ 30	92 (49)	-3.18 (0.72)	-5.57 (0.69)	2.39	0.016*
≥ 29	97 (51)	-3.71 (0.74)	-5.84 (0.69)	2.13	0.033*
≥ 28	105 (56)	-3.61 (0.71)	-5.72 (0.68)	2.11	0.030*
≥ 27	110 (58)	-3.93 (0.72)	-5.87 (0.68)	1.94	0.046*
≥ 26 (>25)	116 (61)	-4.82 (0.73)	-5.98 (0.72)	1.16	0.250

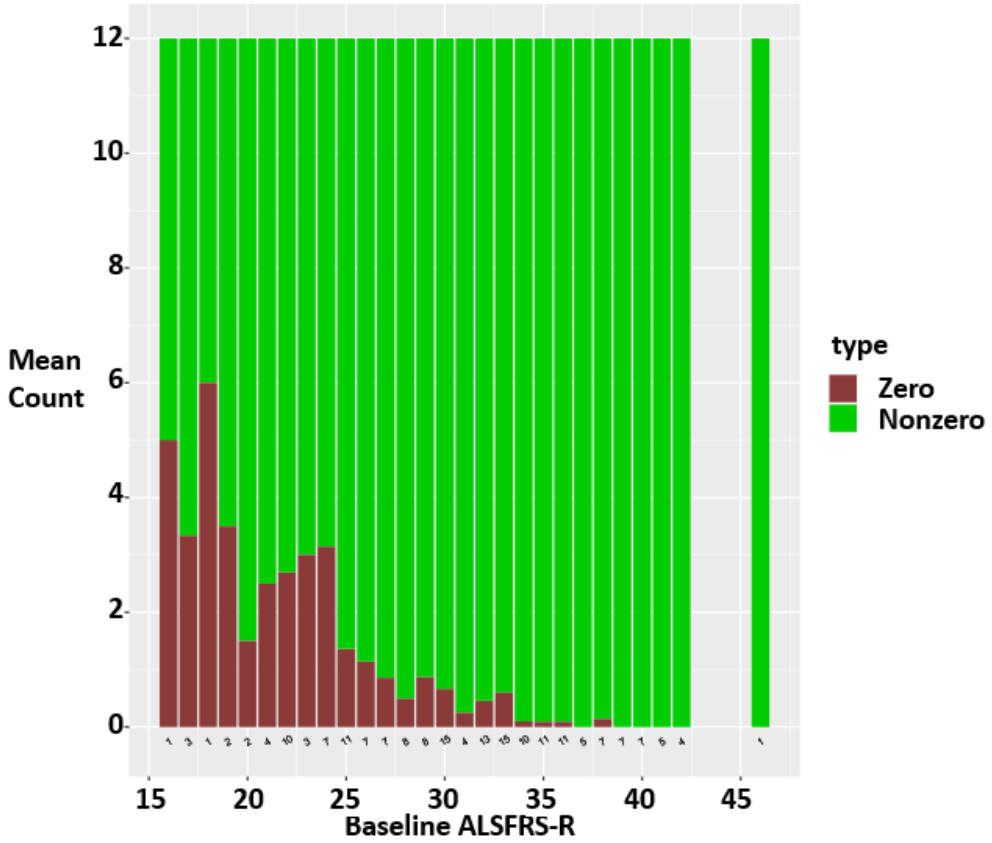


Consistent preservation of function across baseline thresholds

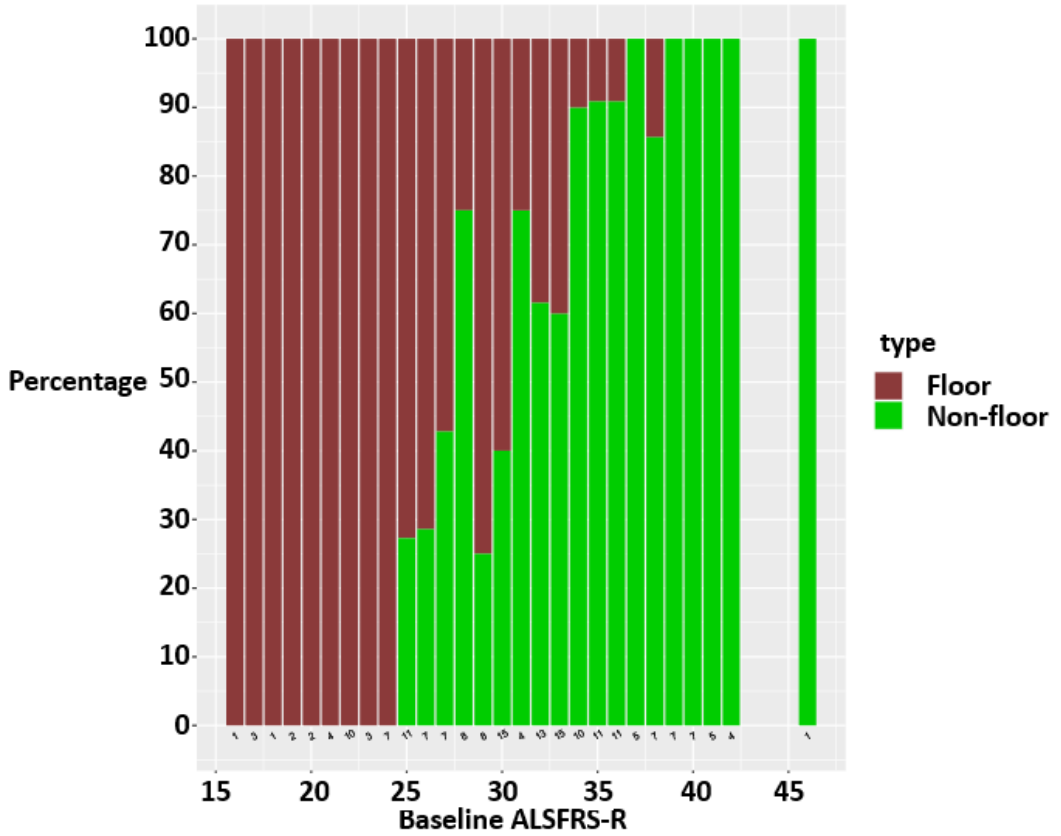
Data on file, Brainstorm, *p ≤ 0.05

Participants with Lower Baseline ALSFRS-R Scores Had Greater Issues with Floor Effect; Decreased with Higher Baseline ALSFRS-R Scores

Average number of ALSFRS-R scale items with value of 0 at baseline, by baseline score



% participants with at least 1 ALSFRS-R scale item with a value of zero at baseline, by baseline score

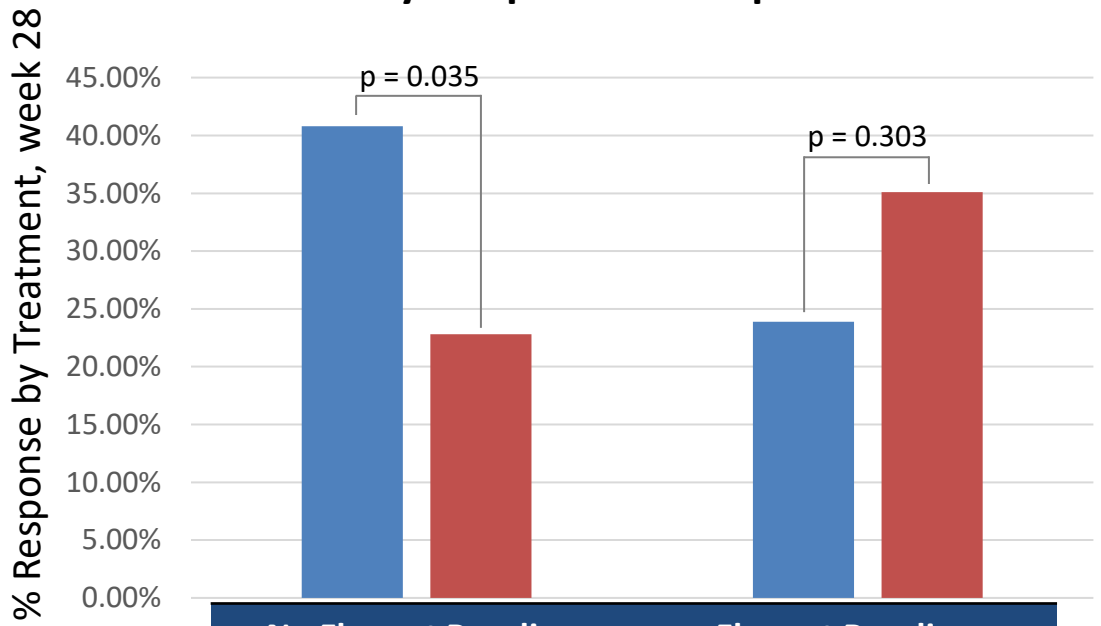


Floor Effect at baseline

No Floor Effect at baseline

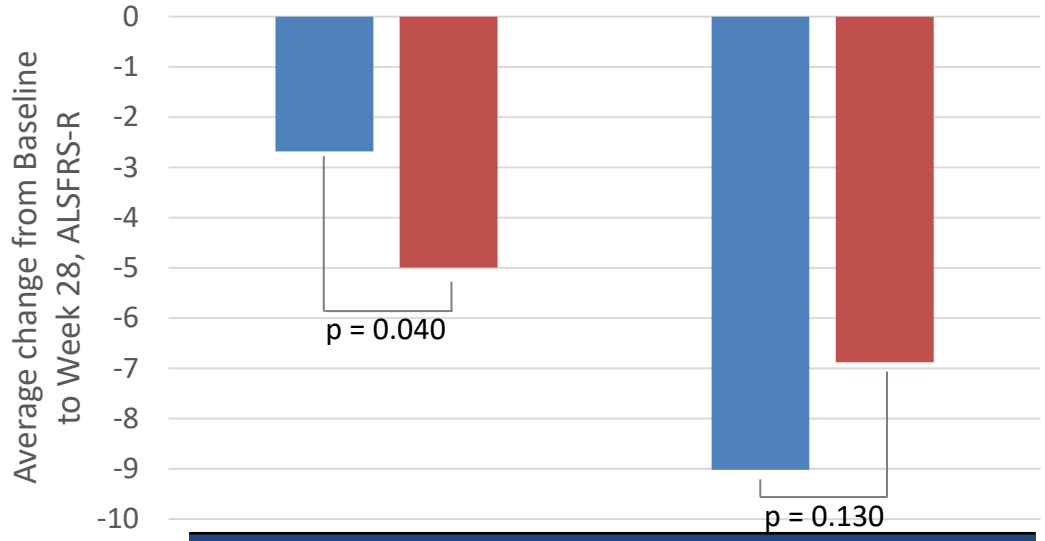
Participants Receiving NurOwn with No Evidence of Floor Effect at Baseline Suggests Treatment Effect

Primary Endpoint: % Response at week 28



	No Floor at Baseline (n=106)	Floor at Baseline (n=83)
NurOwn	40.80%	23.90%
Placebo	22.80%	35.10%
Difference	18%	-11.2%

Secondary Endpoint: Average Change from baseline to Week 28, ALSFRS-R



	No Floor at Baseline (n=106)	Floor at Baseline (n=83)
NurOwn	-2.68	-9.02
Placebo	-4.99	-6.88
Difference	2.31	-2.14

Nominal p-values reported

Biomarker Analysis Methods

- **7 CSF samples over 20 weeks - collected prior to and after each treatment**
  - Validated assays at Thermo Fisher, Quanterix, Olink, Ray Biotech and Norgen
  - Biomarker Statistical Analysis Plan submitted to FDA before trial unblinding
  - Due to skewness in the distribution, biomarker data are log transformed for statistical analysis

<u>Two Main Analyses</u>

1. **Individual Biomarker Trajectories -** plotted using an MMRM model
2. **Prediction of NurOwn Response** - mixed stepwise regression model selected significant biomarkers predicting response to NurOwn.
   → **Clinical outcome based on a post treatment change (rate of decline):** piecewise slope[a]
   → **Pre-specified in the biomarker SAP**

[a] Muggeo & Adelfio, 2011, powerful model which jointly borrows information available from the pre-treatment period to better characterize the slope post-treatment

Pre-specified biomarkers passed validation and were analyzed

16 Neuroinflammatory/Anti-inflammatory markers:

Inflammation: CHI3L1/YKL-40, Chitotriosidase-1, ICAM-1, IP-10, MCP-1, OPG, S100B, SDF-1a, TREM-2, GFAP
Anti-inflammation: Fetuin-A, IL-37, LAP/TGFβ1, MSR1, miR 146a, miR 146b

8 Neurodegeneration markers:

Caspase-3, DR6, miR 142-5p, NfL, pNfH, Tau, TWEAK, UCH-L1

9 Neuroprotection markers:

BDNF, Clusterin/ApoJ, Galectin-1, G-CSF, GDF-15, HGF, LIF, NMNAT1, VEGF-A

- Only biomarkers that passed validation at the time of analyses were included. Additional samples were sent for analysis for each biomarkers that didn't pass validation and were included in analyses once available.
- Biomarkers that have >20% missing data are not included in the multivariate analyses (stepwise model selection)*

* Includes 5 biomarkers: Neuroinflammatory (OPG, miR 146a, miR 146b), Neurodegenerative (miR142-5p) and Neuroprotective (LIF)

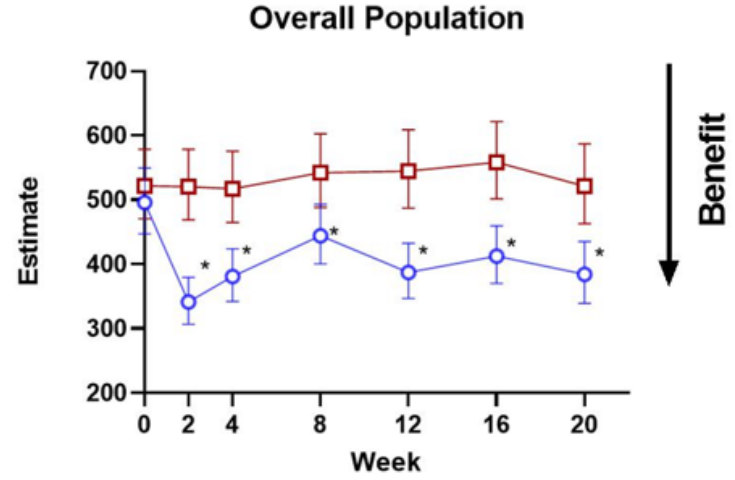
Treatment with NurOwn significantly elevates markers of neuroprotection, and lowers markers of neuroinflammation and neurodegeneration compared to placebo

Primary Biomarker Pathway	Number of Biomarkers	Biomarkers with overall significant treatment effect or treatment by time effect n (%)‡
		All participants
Neuroinflammation	16	10 (62.5%)
Neurodegeneration	8	3 (37.5%)
Neuroprotection	9	7 (77.8%)

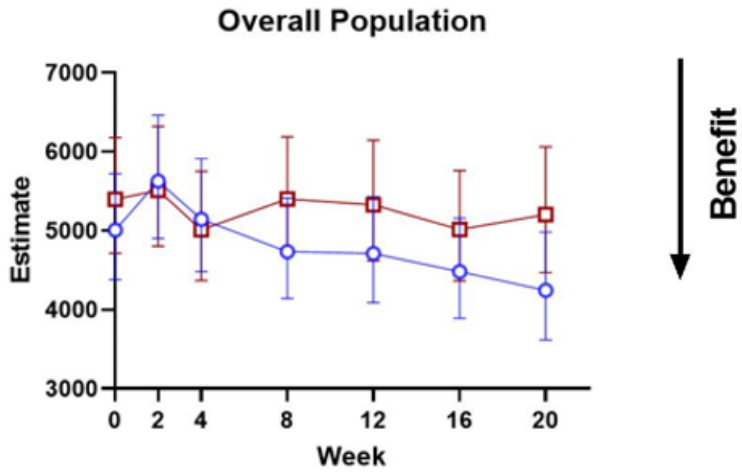
‡<.05, *dependent variable: change in biomarker

NurOwn Improves Biomarkers Across Multiple Pathways Over Time, LS Mean (95%CI)

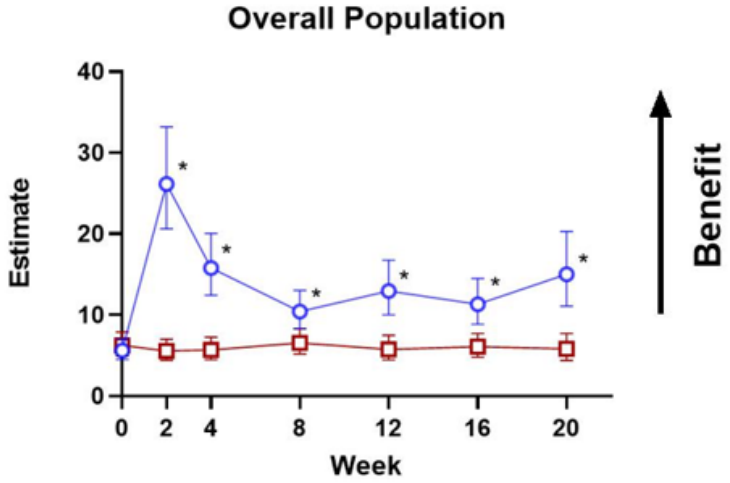
MCP-1 (Pro-Inflammatory)



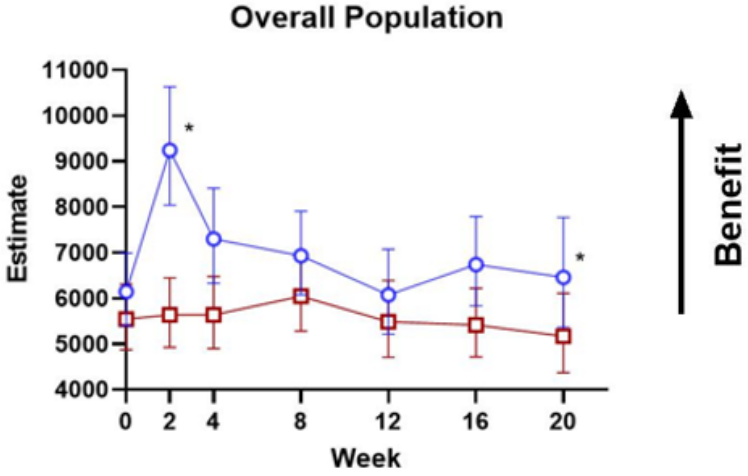
NfL (Neurodegenerative)



VEGF (Neuroprotective)



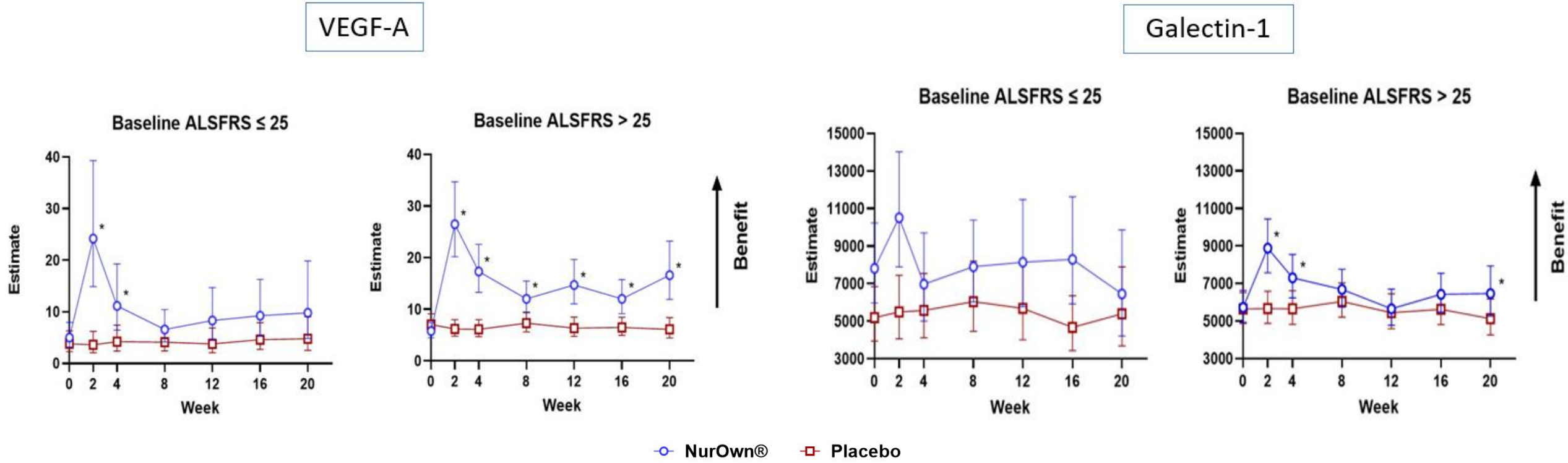
Galectin-1 (Neuroprotective)



NurOwn® Placebo

*p < 0.05, based on change from baseline

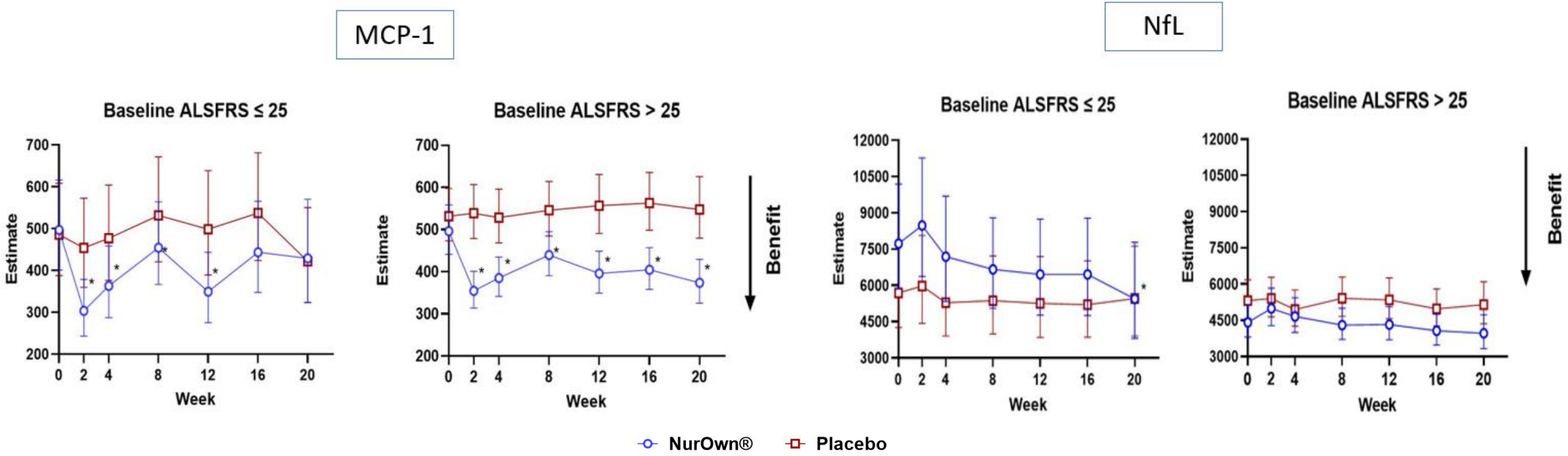
Biomarker data reveal NurOwn biologically active in all trial participants, not impacted by floor observed with ALSFRS-R



- Neuroprotection: Rapid increase with NurOwn in both subgroups relative to placebo, strong treatment effect
- The trend of NurOwn compared to Placebo is generally consistent across the two groups (<=25 and >25)

*p < 0.05, based on change from baseline

Biomarker data reveal NurOwn biologically active in all trial participants, not impacted by floor observed with ALSFRS-R



- Neuroinflammatory Biomarkers: A large reduction in inflammation at Week 2, indicating a treatment effect
- Neurodegeneration: NfL values decreased for NurOwn participants while the placebo group showed a flat trend

*p < 0.05, based on change from baseline

Relationship Between Biomarkers and Clinical Outcomes reveal biomarkers across 3 pathways important to clinical response observed

Clinical outcome based on a post treatment change (rate of decline): piecewise slope

Stepwise Regression Model for NurOwn Group	p-value
Baseline LAP	0.0048
Baseline NfL	<.0001
mean Change Galectin-1	0.0073

- Statistical model identifies 3 biomarker that are predictive of clinical outcomes
- good model fit

Neuroinflammation
Neurodegeneration
Neuroprotection

Summary

- NurOwn marginally better outcomes for primary and key secondary endpoints
  - Non-significant improvement due to confounding floor effect
- NurOwn significantly better outcomes in analyses controlling for floor effect
  - Outcomes align with historical data and power calculations
  - Significance in subgroup of prespecified patients (ALSFRS-R score ≥ 35)
  - Significant results accounting for presence of floor at baseline
- Treatment with NurOwn significantly elevates markers of neuroprotection, and lowers markers of neuroinflammation and neurodegeneration over time compared to placebo
- Statistical modeling identifies biomarkers that have the potential to predict a clinical response with NurOwn, with two different clinical endpoints
- The same biomarker responses, including patterns by treatment, are observed across biomarker pathways in participants with less advanced ALS, and advanced ALS

Manufacturing Sites

City of Hope Center for Biomedicine & Genetics

Dana-Farber Harvard Cancer Center

Cell Manipulation Core

Treatment Centers

University of Massachusetts Medical School

Massachusetts General Hospital

Mayo Clinic

UC Irvine

Cedars-Sinai

Sutter Health
Sutter Pacific Medical Foundation

Funding

CIRM
California's Stem Cell Agency

ALS Association

I AM ALS