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NurOwn® for Treatment of ALS

September 27, 2023

Cellular, Tissue, and Gene Therapies Advisory Committee

Brainstorm Cell Therapeutics

Introduction

Stacy Lindborg, PhD

Co-Chief Executive Officer

Brainstorm Cell Therapeutics

Why We're Here Today

Positive results in prespecified subgroup of early disease participants

+

Supportive Evidence

Biomarker data showed biological effect with NurOwn

Floor effect uncovered data bias

Evidence of positive benefit-risk supports approval

NurOwn Unique Manufacturing Process with Established Quality

- CMC topics referenced in FDA briefing document
  - Some already addressed and for others studies ongoing
- Production process robust and consistent
  - All products produced passed pre-specified criteria for release
    - ~500 products in ~200 people
- Some variability expected in autologous product in cell count

We will work to meet all of FDA's requirements and specifications

FDA Guidances: Importance of Exercising Regulatory Flexibility for Life-Threatening and Severely Debilitating Illness

FDA Regulations Allow Regulatory Flexibility for Life-Threatening and Severely-Debilitating Illnesses

*"**The Food and Drug Administration (FDA) has determined that it is appropriate to exercise the broadest flexibility in applying the statutory standards**, while preserving appropriate guarantees for safety and effectiveness. These procedures reflect the recognition that physicians and patients are generally willing to accept greater risks or side effects from products that treat life-threatening and severely debilitating illnesses, than they would accept from products that treat less serious illnesses. These procedures also reflect the recognition that the benefits of the drug need to be evaluated in light of the severity of the disease being treated."*

-- 21 C.F.R. § 312.80 Subpart E Drugs Intended to Treat Life-Threatening and Severely-Debilitating Illnesses

FDA Has Explained Importance of Regulatory Flexibility for ALS

*"**FDA has long stressed the appropriateness of exercising regulatory flexibility** in applying the statutory standards to drugs for serious diseases with unmet medical needs, while preserving appropriate assurance of safety and effectiveness" … "an objective finding (e.g., muscle strength) **even if of relatively small magnitude** [may] contribute to assessments of benefits and risk"*

-- US Department of Human and Health Services, FDA, CDER and CBER 2019 Amyotrophic Lateral Sclerosis:Developing Drugs for Treatment, Guidance for Industry

NurOwn (MSC-NTF) Novel Cell Therapy for ALS

- Induces autologous, bone marrow-derived, mesenchymal stem cells (MSCs) to secrete neurotrophic factors (NTFs)
- Modulates neuroinflammatory and neurodegenerative disease processes
  - Promotes neuronal survival
  - Improves neurological function

NurOwn Designed to Minimize Risk of Adverse Reaction

- Autologous cells recognized as individual's own cells
  - Safer choice in avoiding unwanted immune responses

- Manufacturing process free of
  - Antibiotics
  - Xeno-derived proteins
  - Genetic modifications
  - Viral vectors

NurOwn Delivers Synergistic Benefits of MSC and NTFs to Site of Damage in ALS

MSCs

- Deliver multiple NTFs and immunomodulatory molecules in close proximity to the site of damage
- ALS mouse model[1]
  - Delay motor neuron degeneration
  - Improve motor performance
  - Prolong survival

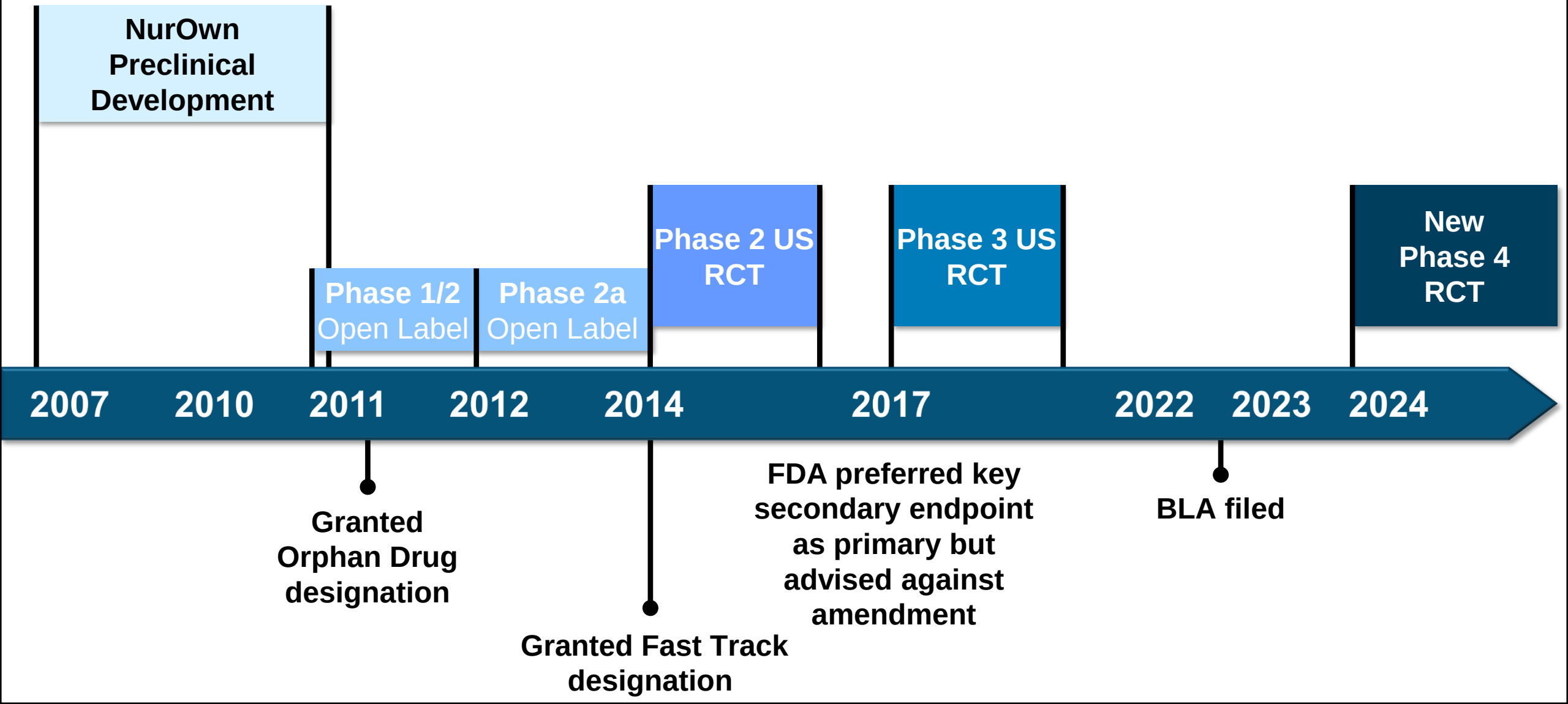
NTFs

- Deficient in several neurodegenerative diseases, including ALS
  - Considered potential therapeutic candidates
- Preclinical studies demonstrated neuroprotective effects of NurOwn[2]
  - Animal models of ALS and other neurodegenerative diseases

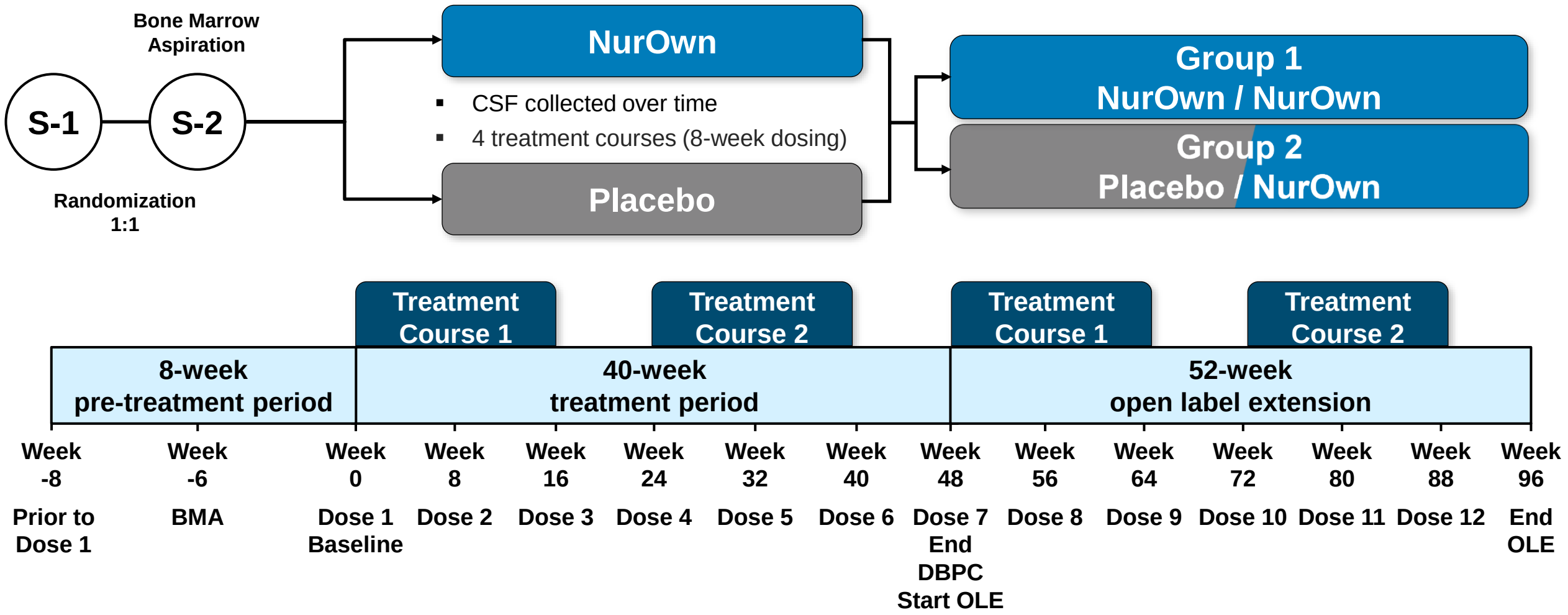
Preclinical data consistent with clinical biomarker findings

1. Forostyak et al., 2011, Marconi et al., 2013, Uccelli et al., 2012; 2. Barhum 2010, Sadan 2009, Sadan 2012, Dadon-Nachum 2011, Levkovitch-Verbin 2010, Perets 2017

NurOwn Clinical and Regulatory History



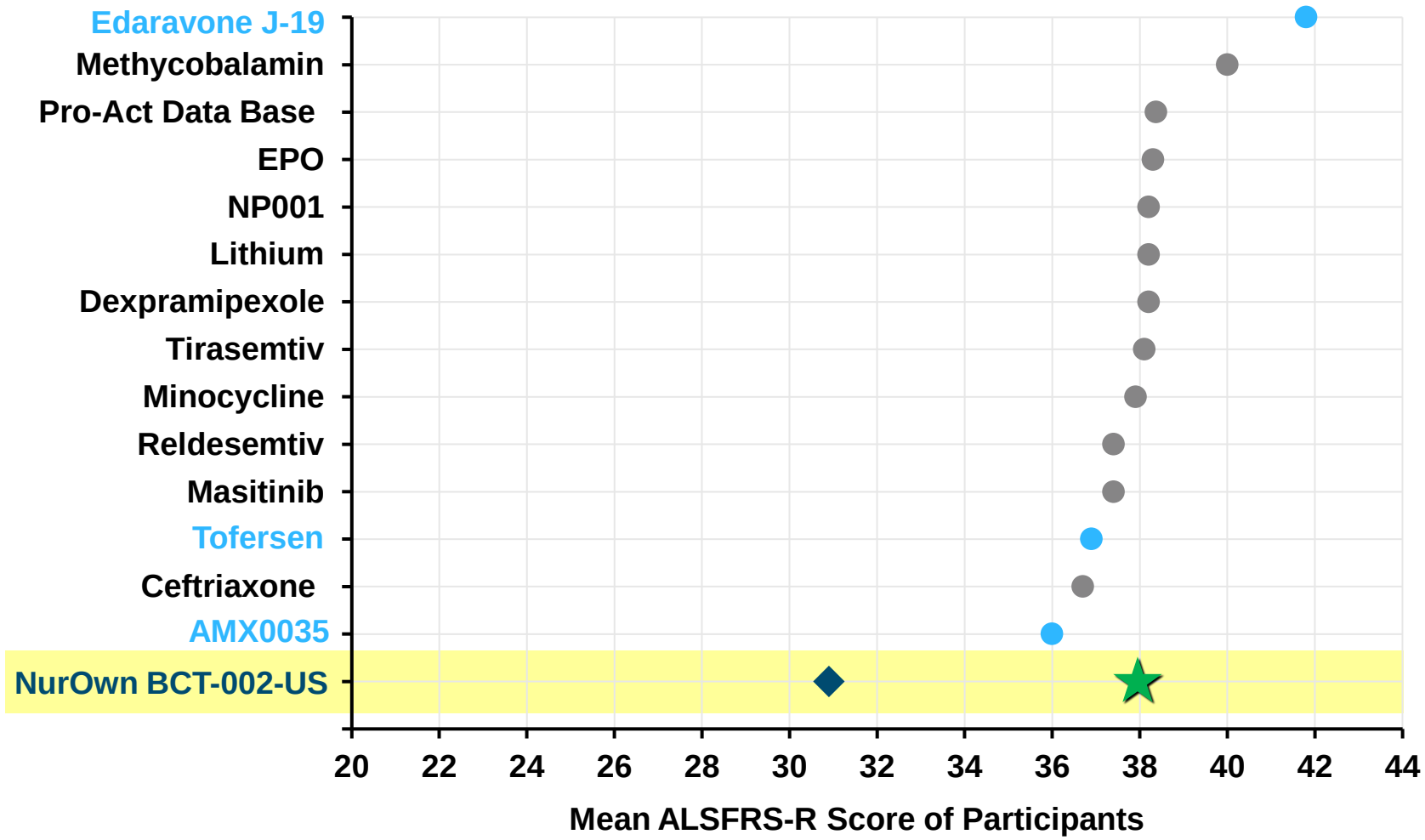
NurOwn Phase 4 Study



Both treatment arms include available standard of care

Phase 3 Enrolled ~ 25% of Participants with Advanced ALS

44 / 189 (23.3%) NurOwn participants with baseline ALSFRS-R ≤ 25 impacted by floor of scale



FDA Approved Therapies

Pre-specified Subgroup (ALSFRS-R ≥ 35)

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*."

Key Conclusions

- ✓ Universally fatal neurodegenerative condition with critical unmet need
- ✓ Endpoints did not reach significance
- ✓ Consistent, clinically meaningful treatment effect with NurOwn in prespecified subgroup with baseline ALSFRS-R scores ≥ 35
- ✓ Supportive results in participants with no floor effect at Baseline
- ✓ Biomarker results support clinical benefit
- ✓ Data support safety of repeat intrathecal administration
- ✓ Positive benefit / risk profile in participants with mild to moderate ALS

Proposed Indication, Administration, and Dosing

Proposed Indication

- Treatment of mild to moderate ALS

Proposed Administration

- Intrathecal injections in CSF by lumbar puncture

Proposed Treatment Course

- 100 to 125 x 10^6 cells with 2 months interval

Agenda

Intro	ALS Landscape and Unmet Need	**Anthony J. Windebank, MD** Professor of Neurology, Judith and Jean Pape Adams Professor of Neuroscience, Mayo Clinic
Efficacy	Phase 3 Results	**Stacy Lindborg, PhD** Co-Chief Executive Officer, Brainstorm
	Consistency and Robustness of NurOwn Treatment Effects	**Lee-Jen Wei, PhD** Professor of Biostatistics Harvard University
	Supportive Clinical Evidence	**Nathan Staff, MD, PhD** Professor of Neurology Research Chair, Department of Neurology, Mayo Clinic
	Supportive Biomarker Evidence	**Robert Bowser, PhD** Chief Scientific Officer, Chair, Department of Translational Neuroscience, Barrow Neurological Institute
Safety	Safety	**Kirk Taylor, MD** Executive Vice President, Chief Medical Officer, Brainstorm
Benefit / Risk	Clinical Perspective	**Anthony J. Windebank, MD** Professor of Neurology, Judith and Jean Pape Adams Professor of Neuroscience, Mayo Clinic

Additional Responders

Donald Berry, PhD
Biostatistician, Founder of Berry Consultants, LLC
Professor, Department of Biostatistics
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Chief Development Officer
Brainstorm Cell Therapeutics

Jesse Cedarbaum, MD
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Professor, Adjunct of Neurology
Yale University School of Medicine

Yossef Levy, PhD
Senior Vice President, Cell Production
Brainstorm Cell Therapeutics

ALS Landscape and Unmet Need

Anthony J. Windebank, MD

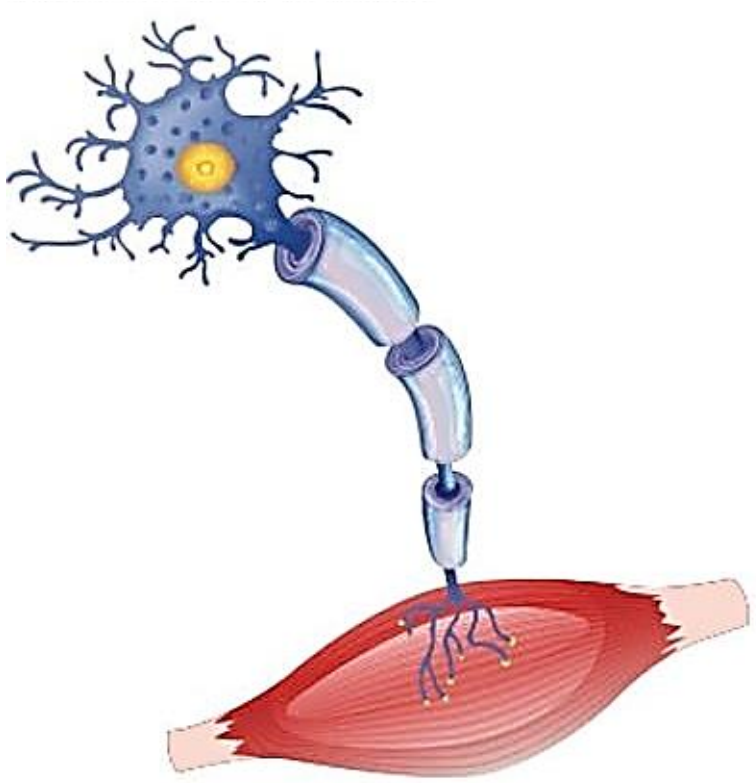
Professor of Neurology

Judith and Jean Pape Adams Professor of Neuroscience

Mayo Clinic

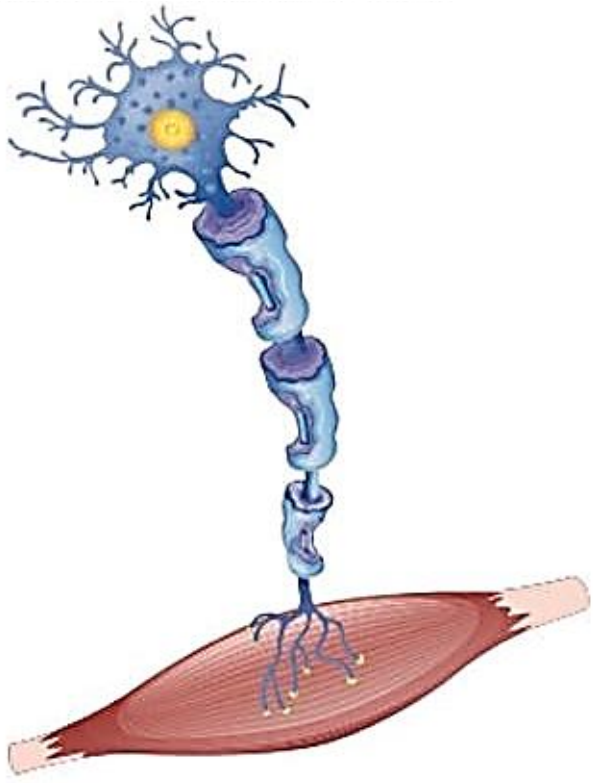
ALS: Devastating, Progressive Neurodegenerative Disease

Normal nerve cell



Muscle contract

Nerve with sclerosis



Muscle unable to contract

- Degeneration and death of motor neurons in brain and spinal cord
- Brain no longer controls muscle actions

ALS Is Uniformly Fatal Disease

People with ALS lose ability to speak, eat, move, and **eventually can't breathe**

Death occurs **2-5 years** from symptom onset generally due to respiratory failure

Too few treatment options for people living with ALS

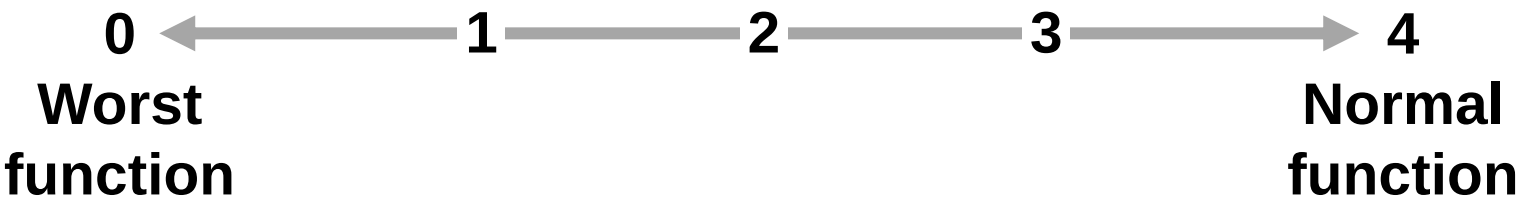
Biological Mechanisms Underlying ALS Are Complex

- Neurodegeneration may be linked to deficient neuroprotection and neuroinflammation[1]
- Stem cell treatment potential to synergistically tackle interrelated pathomechanisms
- MSCs plays key role in immunomodulation

1. Chen, 2020

ALSFRS-R: Primary Tool for Assessing ALS Disease Progression

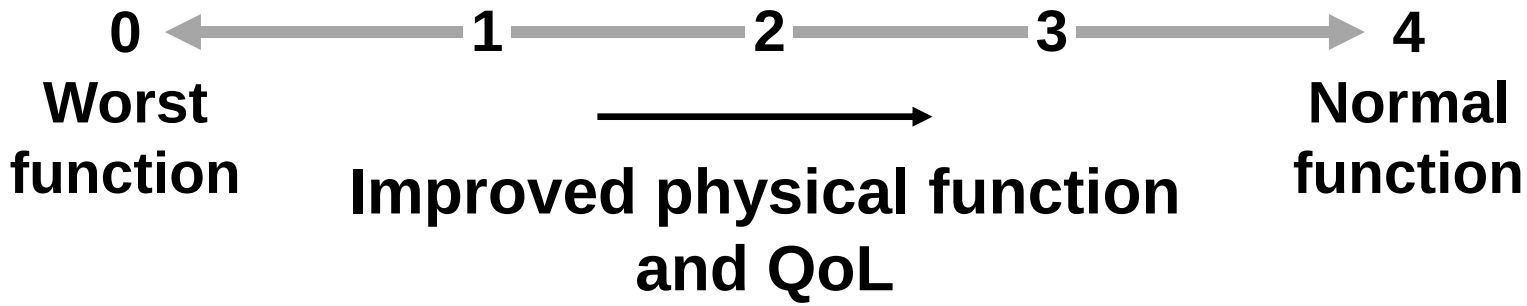
- Primary endpoint in recent FDA regulatory approvals
- 12 functional activities rated 0 – 4



Bulbar	Fine Motor	Gross Motor	Respiratory
Speech	Handwriting	Turning in bed	Dyspnea (difficulty breathing)
Salivation	Cutting food/ using utensils	Walking	Orthopnea (shortness of breath while lying down)
Swallowing	Dressing and hygiene	Climbing stairs	Breathing insufficiency

Every 1-Point Increase in ALSFRS-R Means Improved Physical Function and QoL

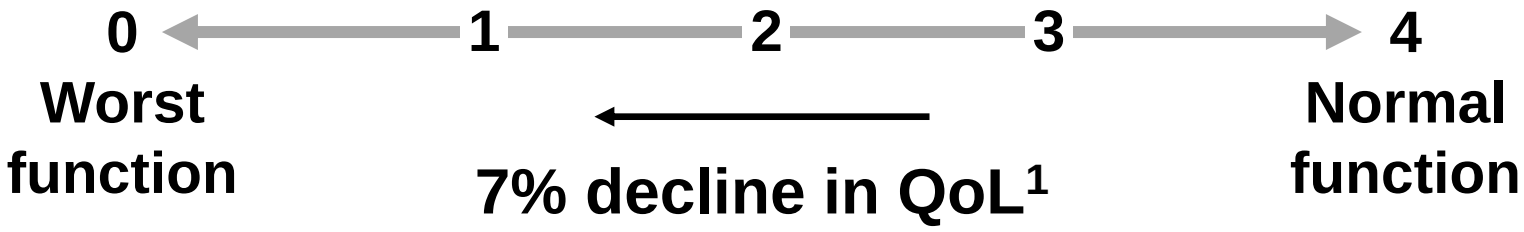
1-point increase



- Examples of one-point difference on ALSFRS-R
  - Ability to turn in bed without assistance
  - Requiring a wheelchair vs walking with assistance
  - Ability of a patient to still feed themself
  - Independence to dress oneself
- Rarely see patients increasing on scale
  - Preservation of function is clinically important

Each 1-Point Decrease Results in Decline in Function and QoL

1-point decrease



- ALSFRS-R most widely used measure
  - Limited by ability to measure changes in physical function with higher and lower function

ALSFRS-R hampered by floor effect, similar to every bounded rating scale[2]

1. Ilse, Soc Indic Res 2015; 2. Hartmaier et al, 2022

Emerging Biomarkers Related to ALS

Neurodegeneration

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

Neuroinflammation

Pro-inflammatory

- CHI3L1 / YKL-40, Chitotriosidase-1, MCP-1, IP-10, OPG, S100B, SDF-1α, TREM-2, GFAP, IL-6, IL-8, miR-155

Anti-inflammatory

- IL-10, Fetuin-A, IL-37, TGF-β1, MSR1, miR-146a-5p, miR-146b-5p

Neuroprotection

- BDNF
- Clusterin / ApoJ
- Galectin-1
- VEGF-A
- G-CSF
- GDF-15
- HGF
- LIF
- NMNAT1
- miR-206

Unmet Need Summary

1. Significant unmet need for more and clinically meaningful treatments that will slow progression of ALS
2. Complex and difficult disease to study
3. Patients need access to promising treatments

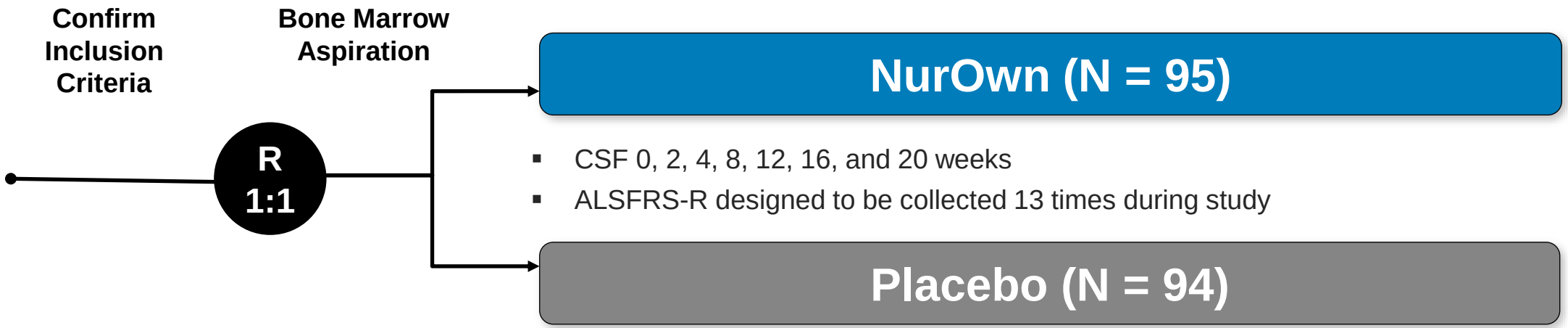
Efficacy

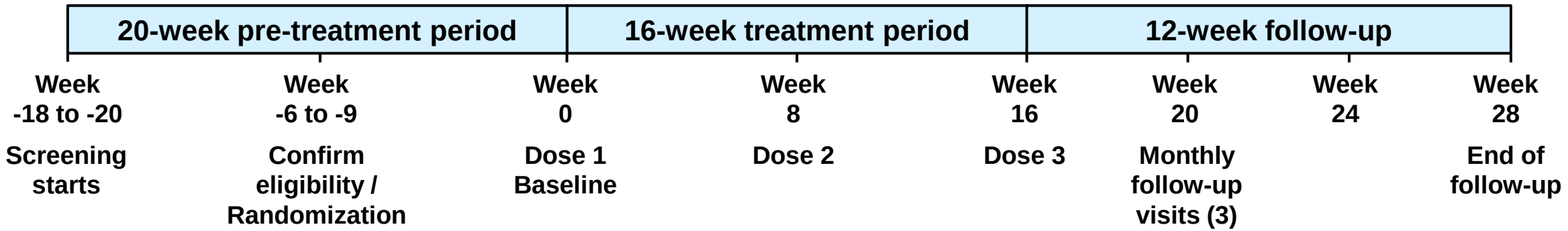
Stacy Lindborg, PhD

Co-Chief Executive Officer

Brainstorm Cell Therapeutics

BCT-002-US: Phase 3 Randomized, Placebo-Controlled, Double-Blind Trial





77% completion rate

Endpoints Selection

Primary Endpoint

- Responder analysis: change in rate of decline as assessed by ALSFRS-R
  - Responder definition: ≥ 1.25 points / month improvement in post-treatment vs pre-treatment slope in ALSFRS-R score at Week 28

Key Secondary Endpoint

- ALSFRS-R change from Baseline to Week 28

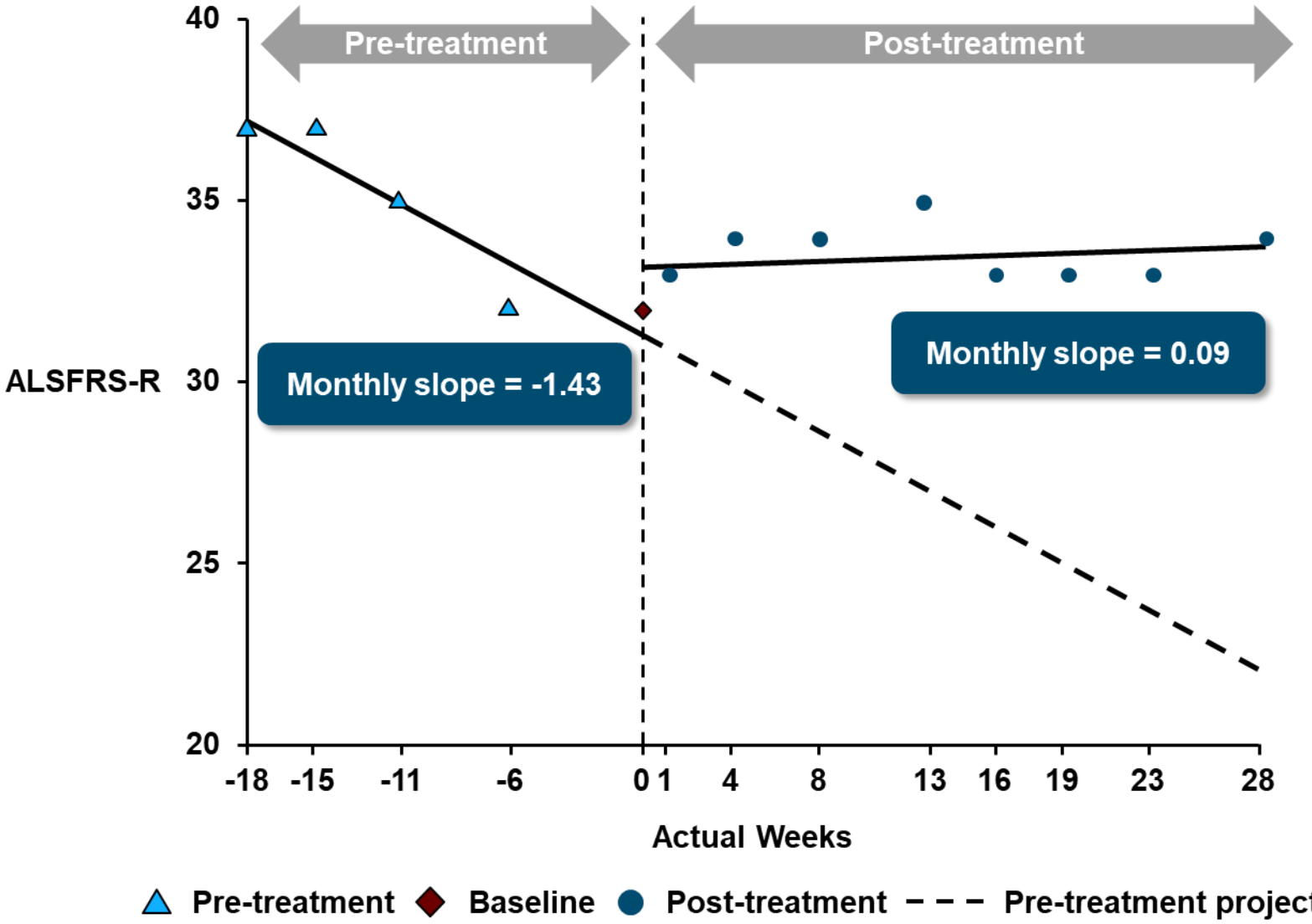
Other Secondary Endpoints

- Response analysis: post-treatment slope improving by ≥ 100%
- CAFS
- SVC change from Baseline to Week 28
- Time to death or tracheotomy
- Time to death due to disease progression
- CSF / blood biomarkers analysis in relationship to clinical efficacy

Prespecified subgroup analysis based on baseline ALSFRS-R threshold ≥ 35

CAFS = Combined Analysis of Function and Survival; SVC = Slow Vital Capacity

Illustration of Clinical Response on Primary Endpoint Using NurOwn Participant Profile from Phase 3 Trial



Threshold for response set to clinically meaningful improvement of ≥ 1.25 points/month

Pre-trt Slope	Post-trt Slope	Difference in Post vs Pre-trt Slope	Responder (difference ≥ 1.25)
-1.43	0.09	1.52	Yes

Responder analysis using logistic regression

Key Inclusion Criteria

- Onset of ALS disease symptoms, including limb weakness within 24 months at Screening Visit
- Upright SVC measure ≥ 65% of predicted for gender, height, and age at Screening Visit
- ALSFRS-R ≥ 25 at Screening Visit (~ 20 weeks prior to Baseline)
- Decline in ALSFRS-R total score of ≥ 3 points in 12 weeks before randomization*

*** Pre-treatment slope or baseline rate of decline was calculated using all data from pre-treatment period**

Baseline Disease Characteristics

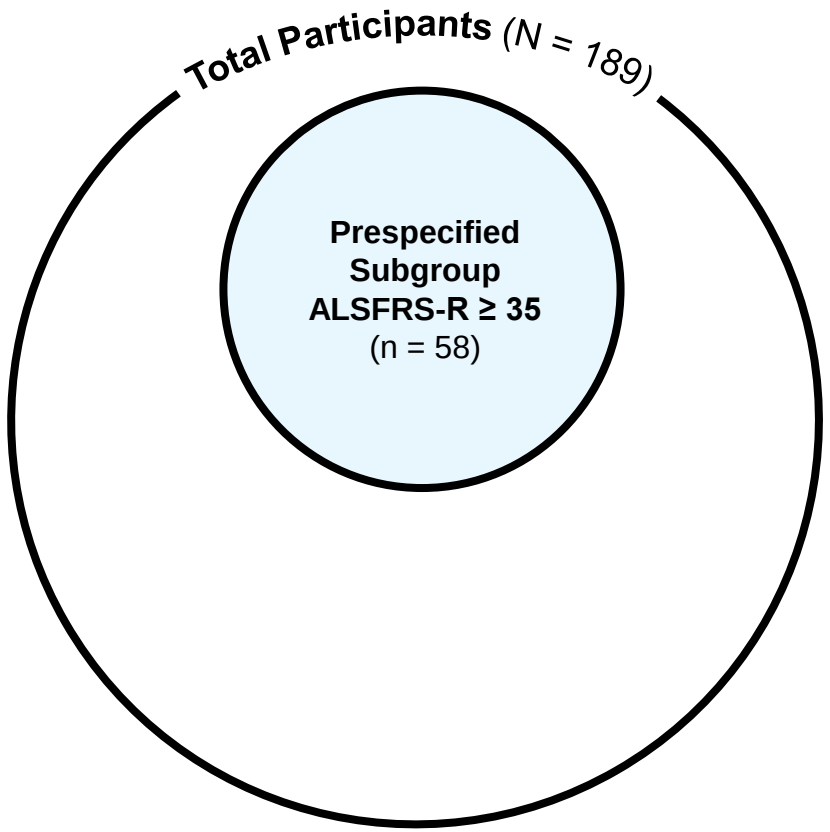
Characteristic	All Participants		ALSFRS-R ≥ 35	
	NurOwn (N = 95)	Placebo (N = 94)	NurOwn (N = 26)	Placebo (N = 32)
Pre-treatment slope, Mean (SD)	**-1.7** (0.8)	**-1.6** (0.8)	**-1.1** (0.6)	**-1.1** (0.5)
Baseline ALSFRS-R, Mean (SD)	**30.3** (6.5)	**31.4** (6.1)	**38.1** (2.8)	**37.9** (2.3)
Months since diagnosis, months, Mean (SD)	**6.8** (4.4)	**6.1** (4.8)	**6.0** (4.5)	**5.5** (4.2)
Months since symptom onset, months, Mean (SD)	**19.6** (5.2)	**19.1** (4.9)	**18.2** (5.3)	**18.5** (4.4)
Use of riluzole, %	**68%**	**60%**	**77%**	**53%**
El Escorial possible, %	**6%**	**6%**	**15%**	**9%**
Lab-supported probable, %	**16%**	**25%**	**39%**	**38%**
Probable, %	**25%**	**33%**	**19%**	**38%**
Definite, %	**53%**	**36%**	**27%**	**16%**
Bulbar, %	**16%**	**22%**	**12%**	**28%**

Endpoint Results in All Participants

	All Trial Participants		
	NurOwn (N = 95)	Placebo (N = 94)	p-value
Primary endpoint, %	**33%**	**28%**	**0.45**
Key secondary endpoint, LS mean	**-5.5**	**-5.9**	**0.69**
Secondary endpoints			
≥ 100% improvement in ALSFRS-R slope through Week 28, %	**14%**	**14%**	**0.99**
CAFS, average rank at Week 28	**73.7**	**72.2**	**0.80**
SVC, % mean change from BL	**-13%**	**-12%**	**0.56**
Events (Event free probability) for death due to any cause through Week 28, n **(%)**	10 **(88%)**	2 **(98%)**	**0.347***
Events (Event free probability) for death due to disease progression through Week 32, n **(%)**	8 **(90%)**	3 **(92%)**	**0.209***
Events (Event free probability) for death due to any cause through Week 32, n **(%)**	10 **(88%)**	4 **(89%)**	**0.106***

*** p-value from prespecified Cox proportional hazards model; Note: Results from secondary endpoints through Week 32 do not include two deaths that occurred in participants randomized to placebo which occurred prior to treatment**

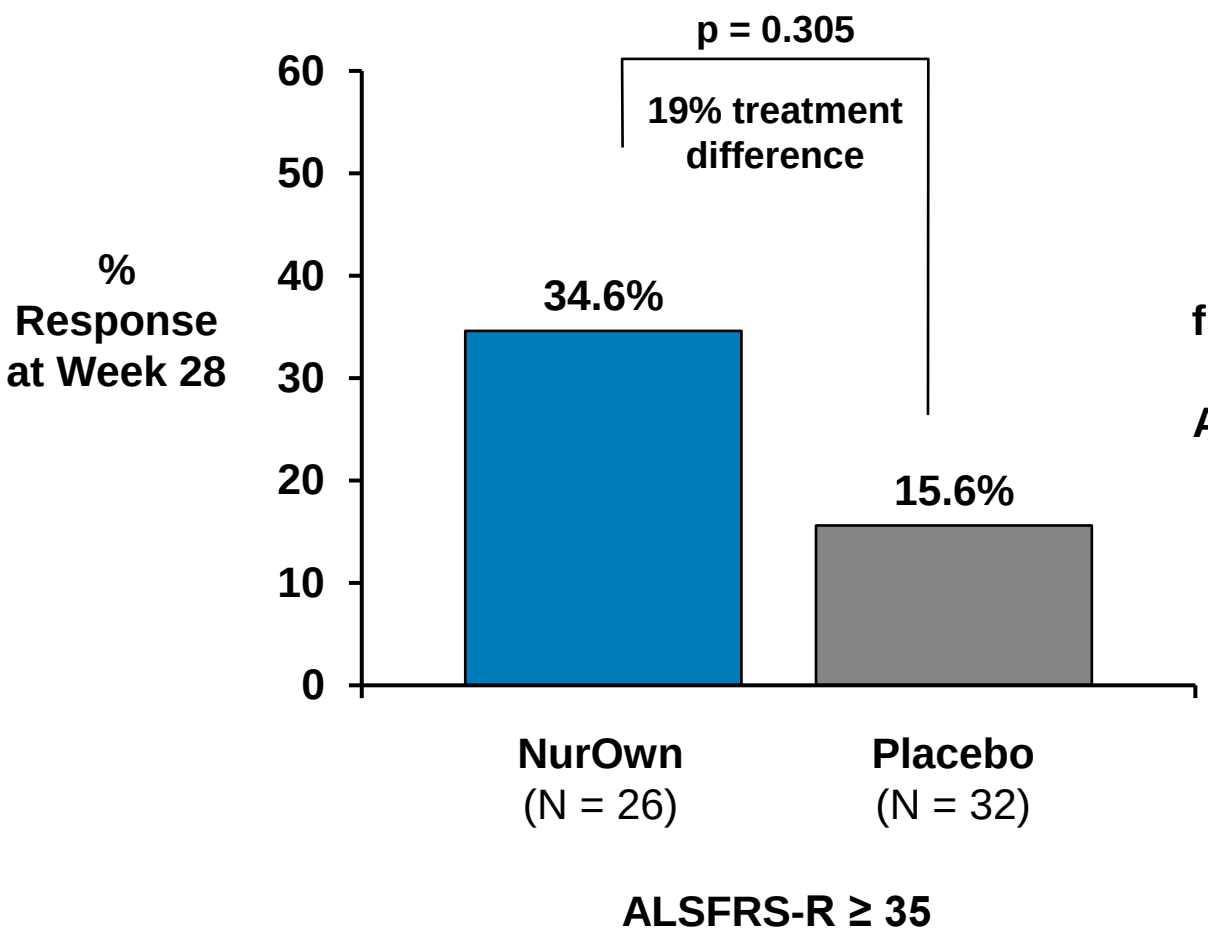
Treatment Effect Evident in Pre-Specified Subgroup with Baseline ALSFRS-R ≥ 35



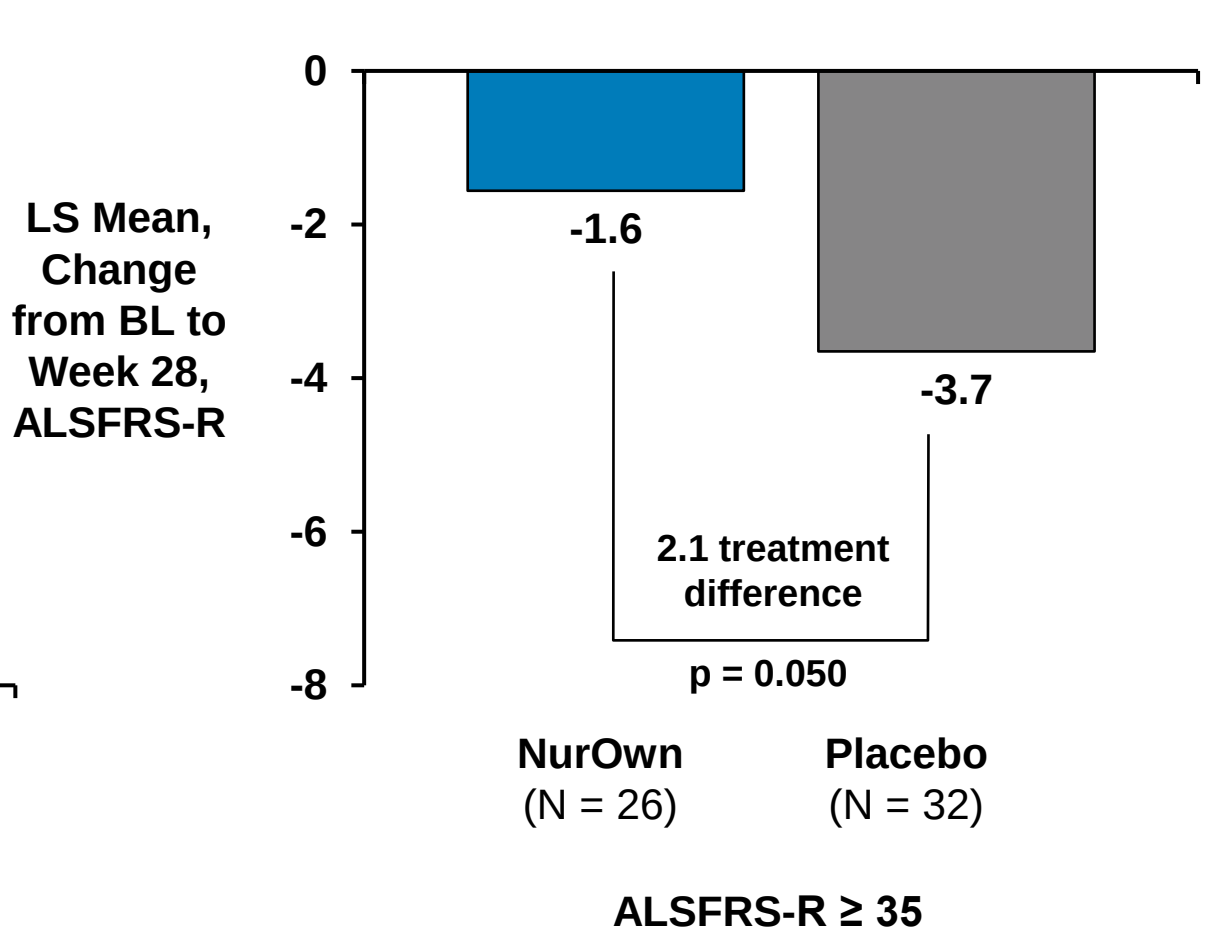
- 31% of participants with baseline ALSFRS-R ≥ 35
  - NurOwn (n = 26)
  - Placebo (n = 32)

NurOwn Showed Clinically Meaningful Response on Prespecified Subgroup ALSFRS-R ≥ 35

Primary Endpoint

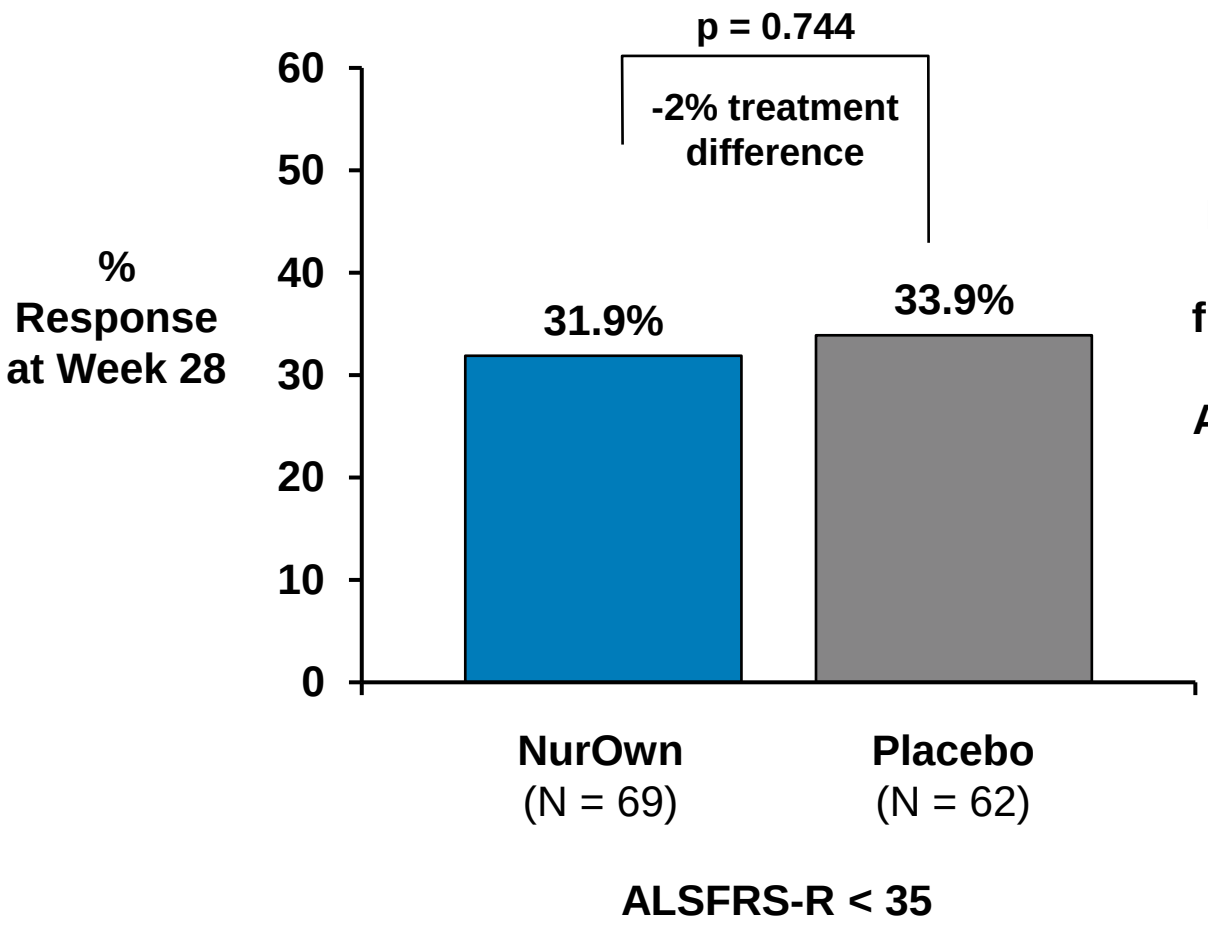


Key Secondary Endpoint

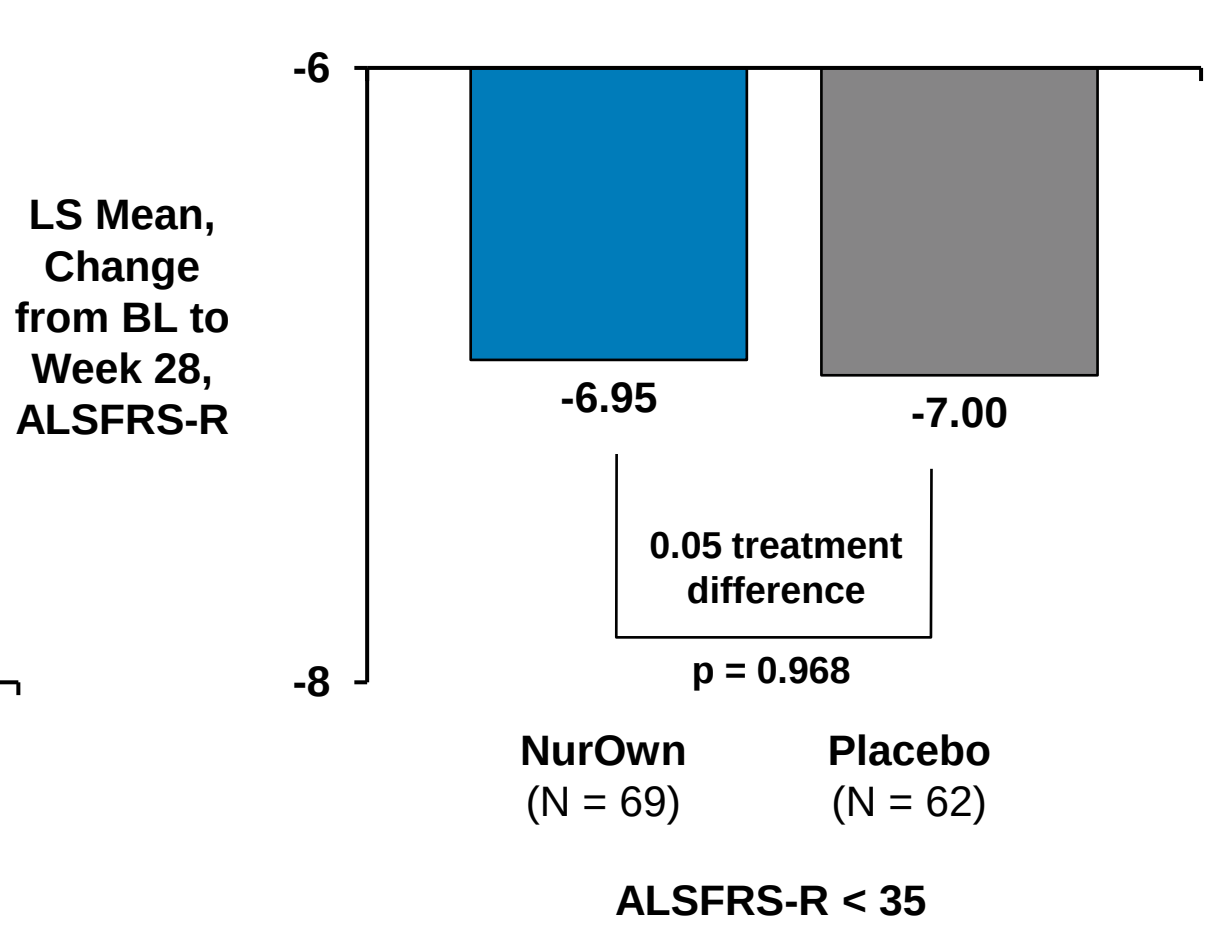


No Treatment Difference in Prespecified Subgroup ALSFRS-R < 35

Primary Endpoint



Key Secondary Endpoint



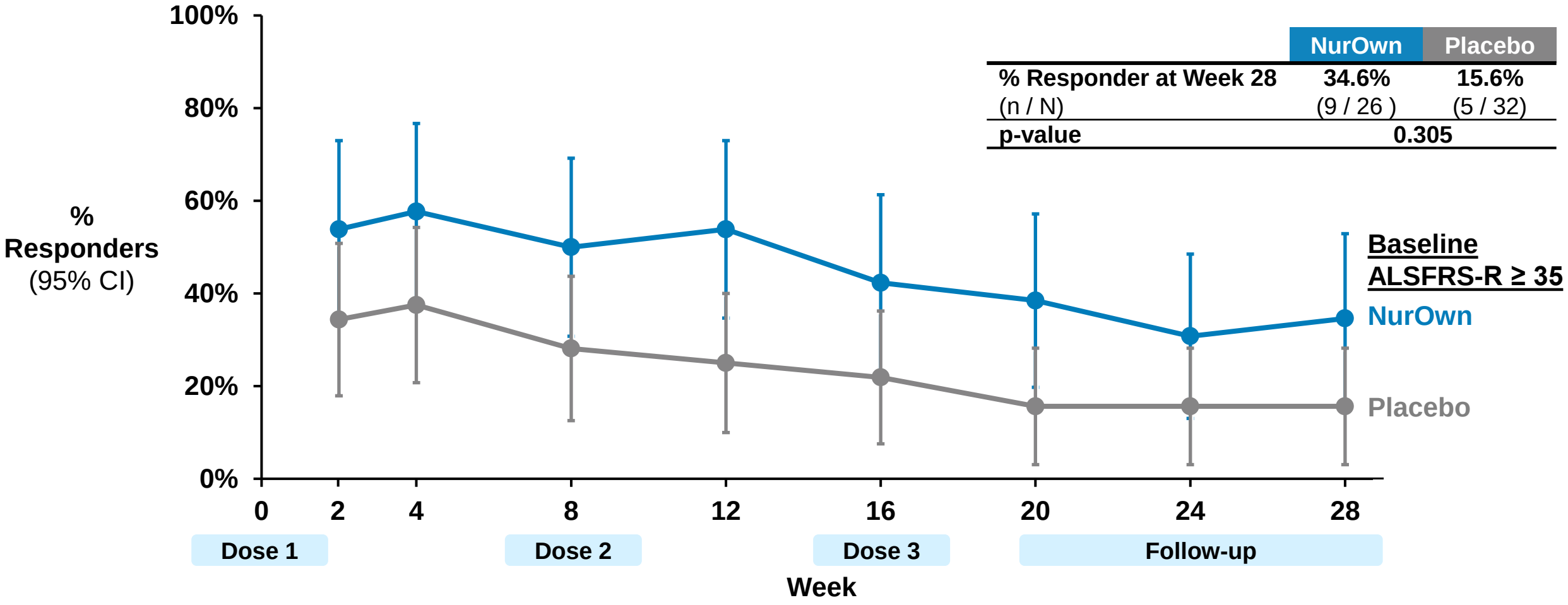
NurOwn Shows Treatment Effects Across Secondary Endpoints in Participants with ALSFRS-R ≥ 35

Secondary Endpoints	ALSFRS-R ≥ 35		p-value
	NurOwn (N = 26)	Placebo (N = 32)	
≥ 100% improvement in ALSFRS-R slope through Week 28, n (%)	7 **(27%)**	5 **(16%)**	**0.47**
CAFS, average rank at Week 28	**93.7**	**78.3**	**0.10**
Events (Event free probability) for death due to disease progression through Week 32, n (%)	0 **(> 99%)**	0 **(> 99%)**	**NA***
Events (Event free probability) for death due to any cause through Week 32, n (%)	0 **(> 99%)**	1 **(90%)**	**NA***

*** p-value from a prespecified Cox proportional hazards model in SAP. NA: p-value not estimable due to lack of events.**

NurOwn Shows Treatment Effects Over Time on Primary Endpoint in Participants with ALSFRS-R ≥ 35

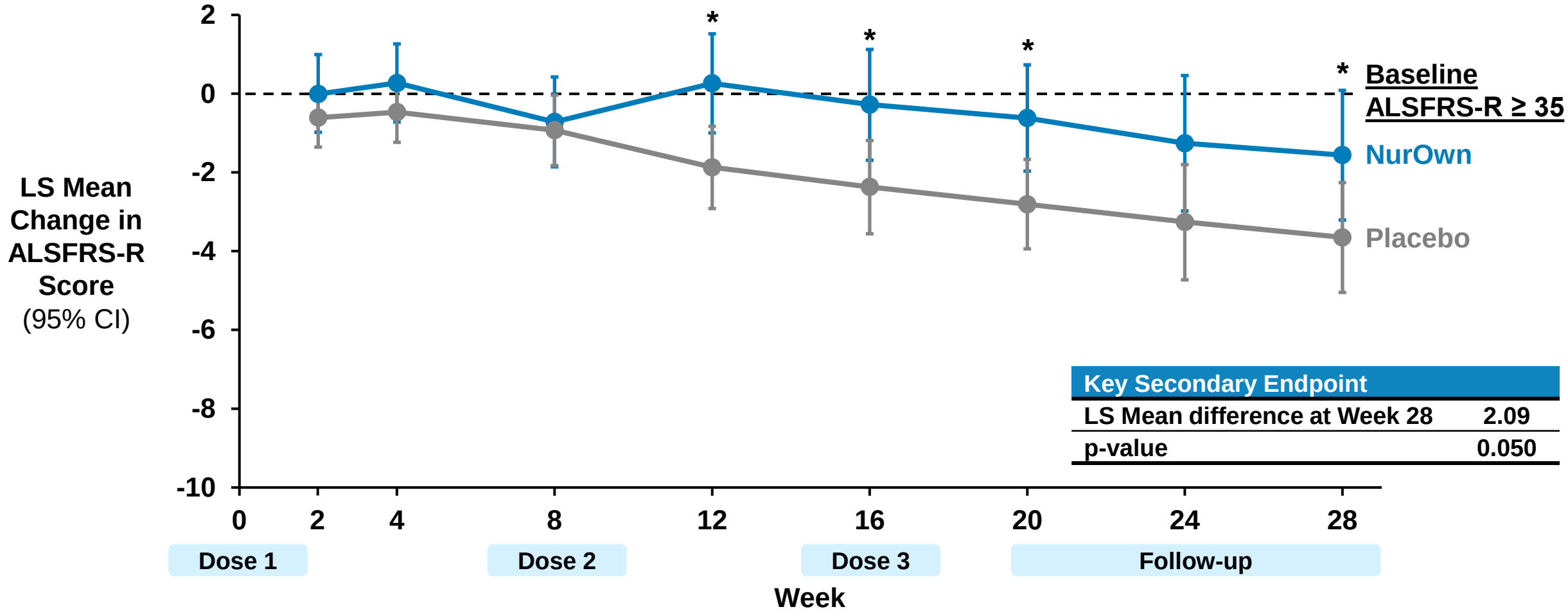
Statistically significant treatment difference observed early and consistent across trial



	NurOwn	Placebo
% Responder at Week 28	34.6%	15.6%
(n / N)	(9 / 26)	(5 / 32)
p-value	0.305	

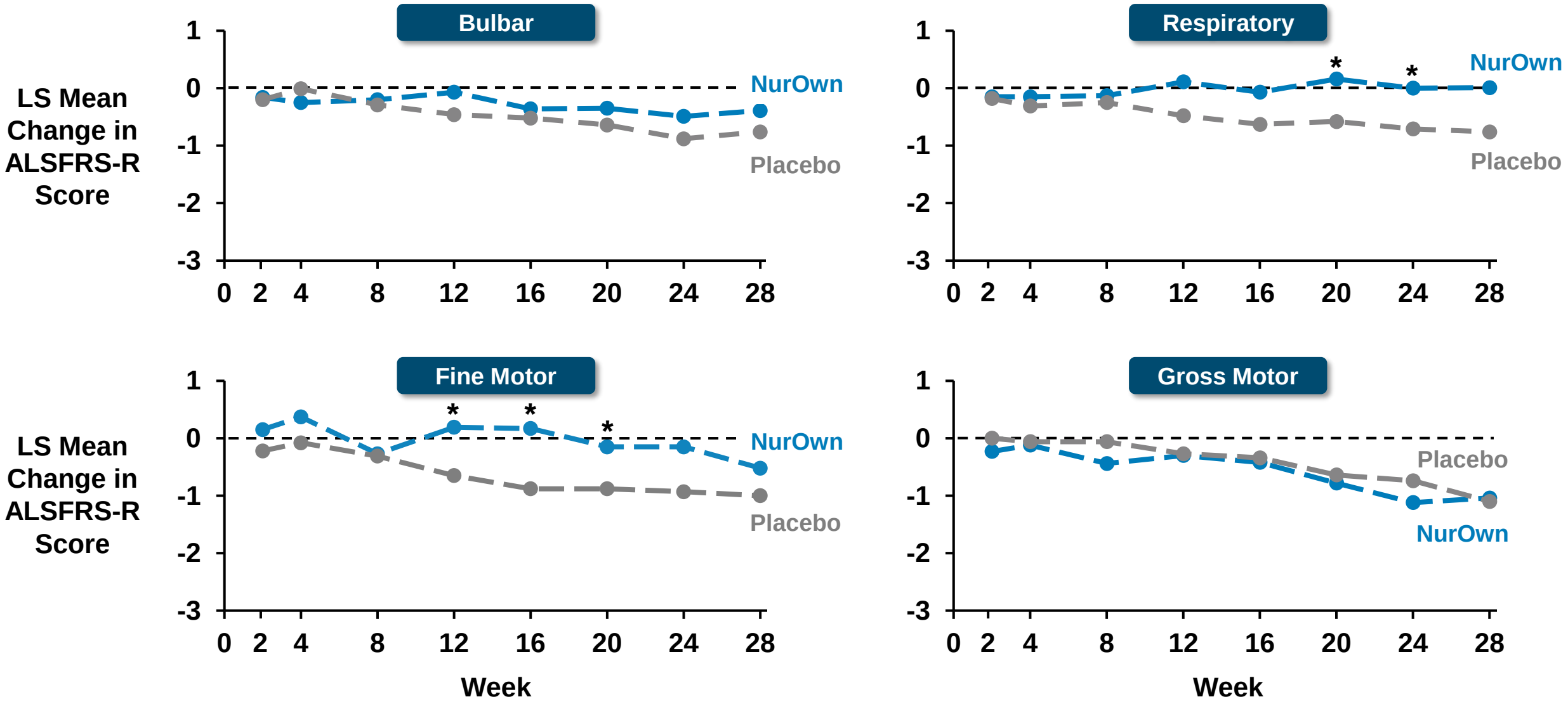
Responder ≥ 1.25 points/month improvement in post-treatment vs pre-treatment slope in ALSFRS-R score

NurOwn Shows Treatment Effects Over Time on Key Secondary Endpoint in Participants with ALSFRS-R ≥ 35



* p ≤ 0.05

NurOwn Treatment Effect on ALSFRS-R Driven by Multiple Subscales in Participants with ALSFRS-R ≥ 35



* p ≤ 0.05

Consistency and Robustness of NurOwn Treatment Effects in Prespecified Subgroup

Lee-Jen Wei, PhD

Professor of Biostatistics

Harvard University

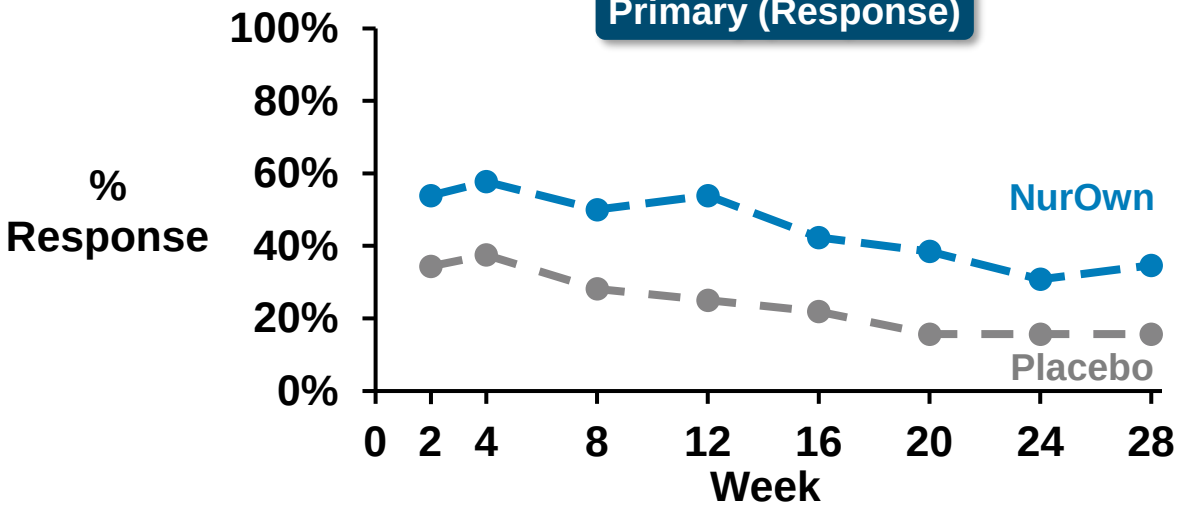
How Robust and Consistent Are Data to Justify NurOwn Treatment Benefit for Less Advanced Patients?

- For each patient, multiple outcomes are collected
  - Reflect overall disease burden / progression evaluated from various angles and perspectives
- How can multiple outcomes be used to assess global treatment effect beyond using endpoints at one time point for decision making?
  - Consistency of changes over time across ALSFRS-R subscales
  - Consistency of changes across four clinical endpoints
- Use this approach to explore how robust and consistent data are in the pre-specified subgroup

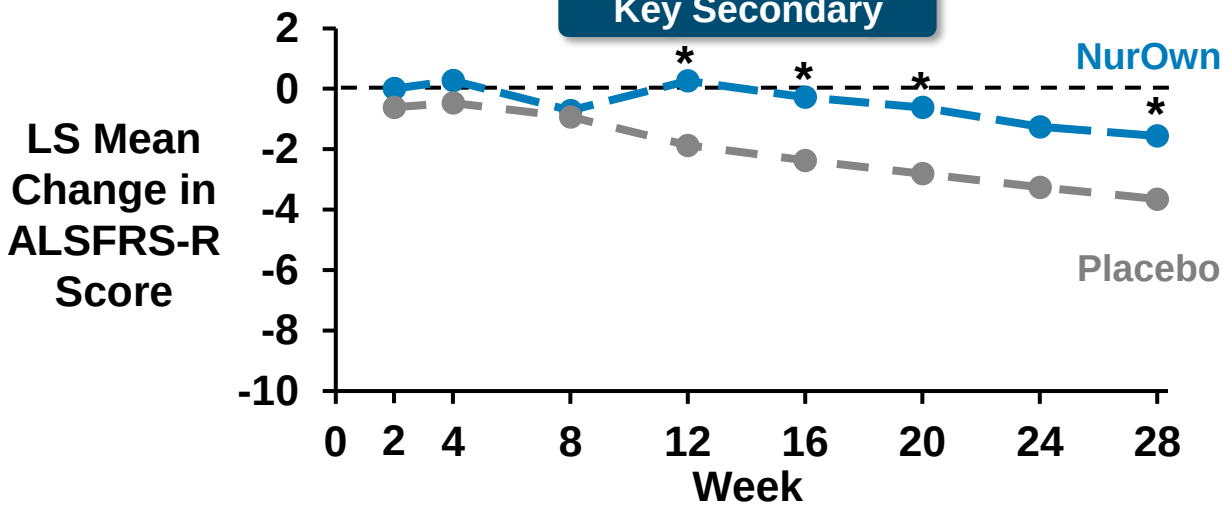
Li et al., 2020

NurOwn Temporal Treatment Effects Sustained Over Entire Study Period (Baseline ALSFRS-R ≥ 35)

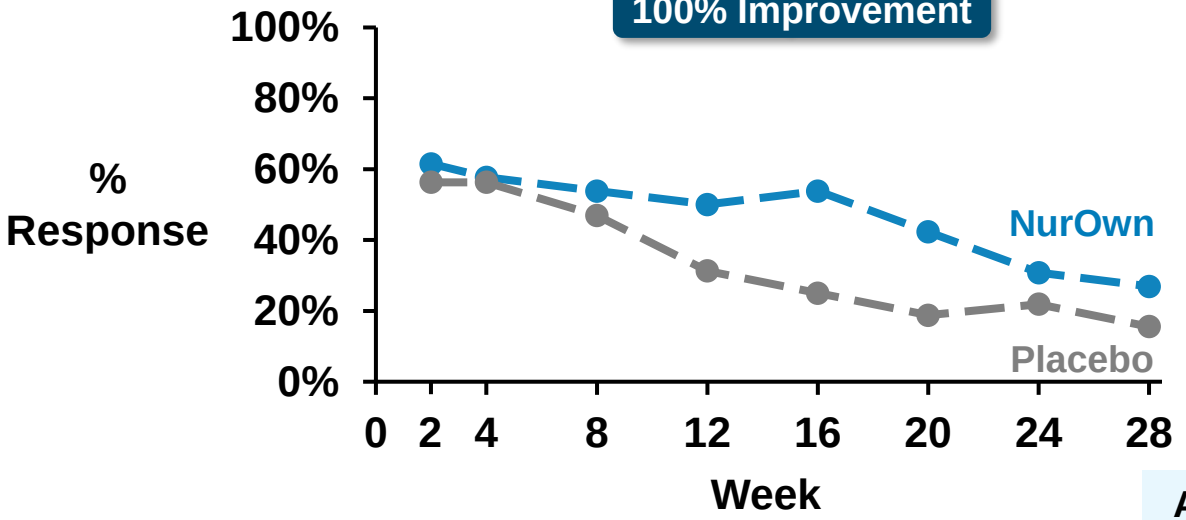
Primary (Response)



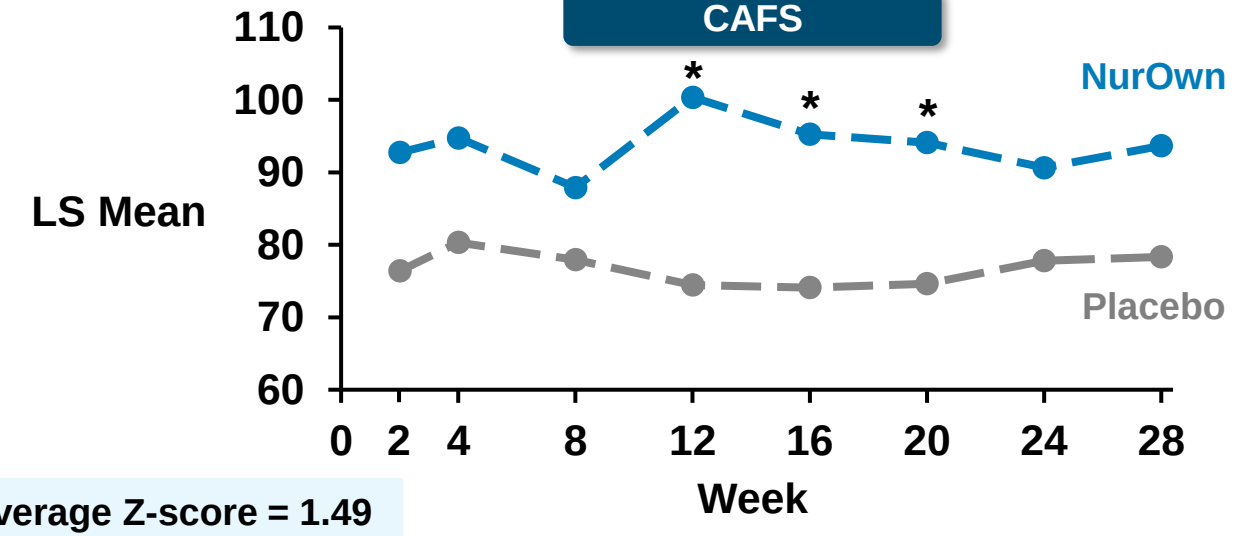
Key Secondary



100% Improvement



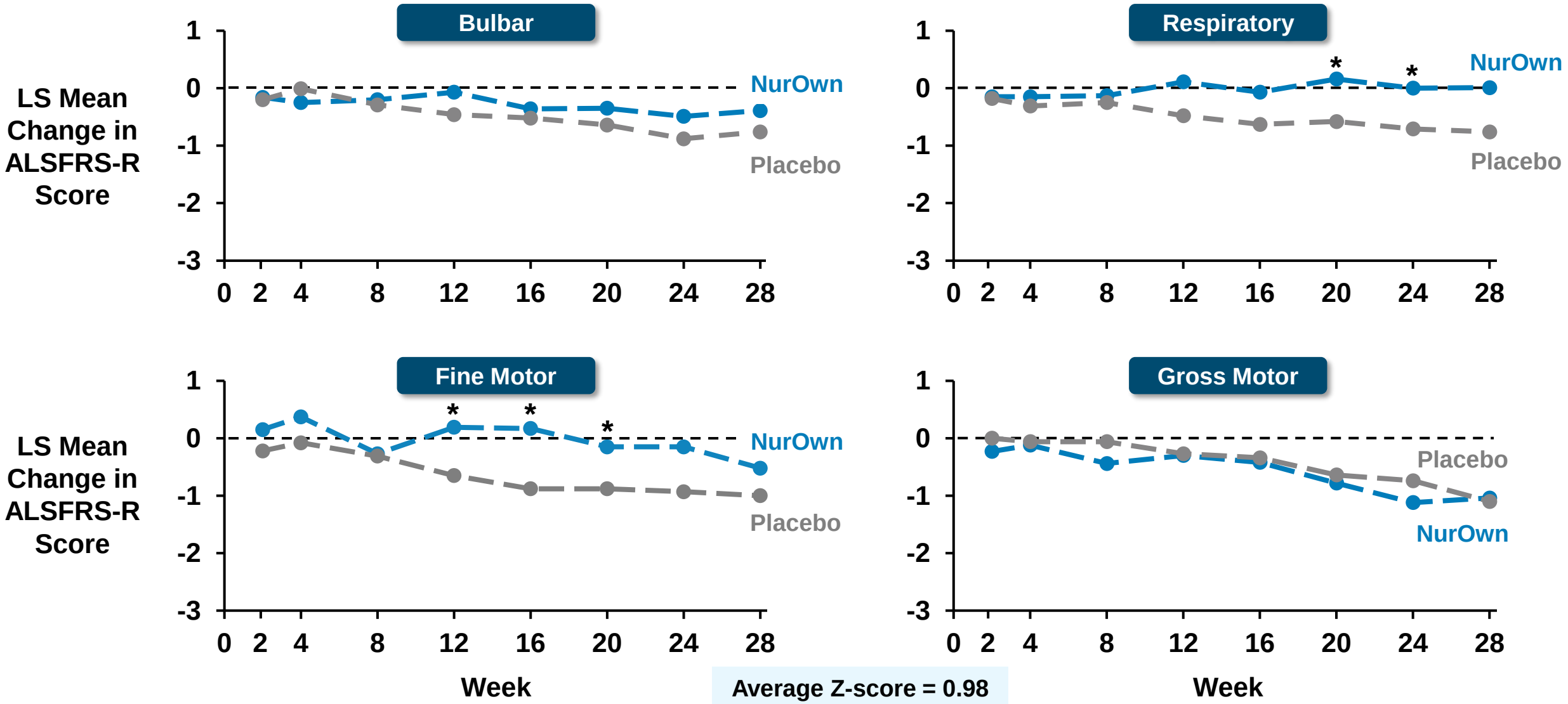
CAFS



Average Z-score = 1.49
p = 0.021

* p ≤ 0.05

NurOwn Temporal Treatment Effects Sustained Across ALSFRS-R Subscales (Baseline ALSFRS-R ≥ 35)



Average Z-score = 0.98
p = 0.045

* p ≤ 0.05

Summary of Totality and Consistency of Treatment Effects

1. Consistent and robust treatment effect in prespecified subgroup
2. Treatment effect also observed consistently across various subgroups, including defined by median ALSFRS-R score of trial
3. Totality of evidence showed significant effect across subscales and endpoints
4. Observed treatment benefits likely driven by true treatment effects; not spurious finding

Supportive Clinical Evidence

Nathan Staff, MD, PhD

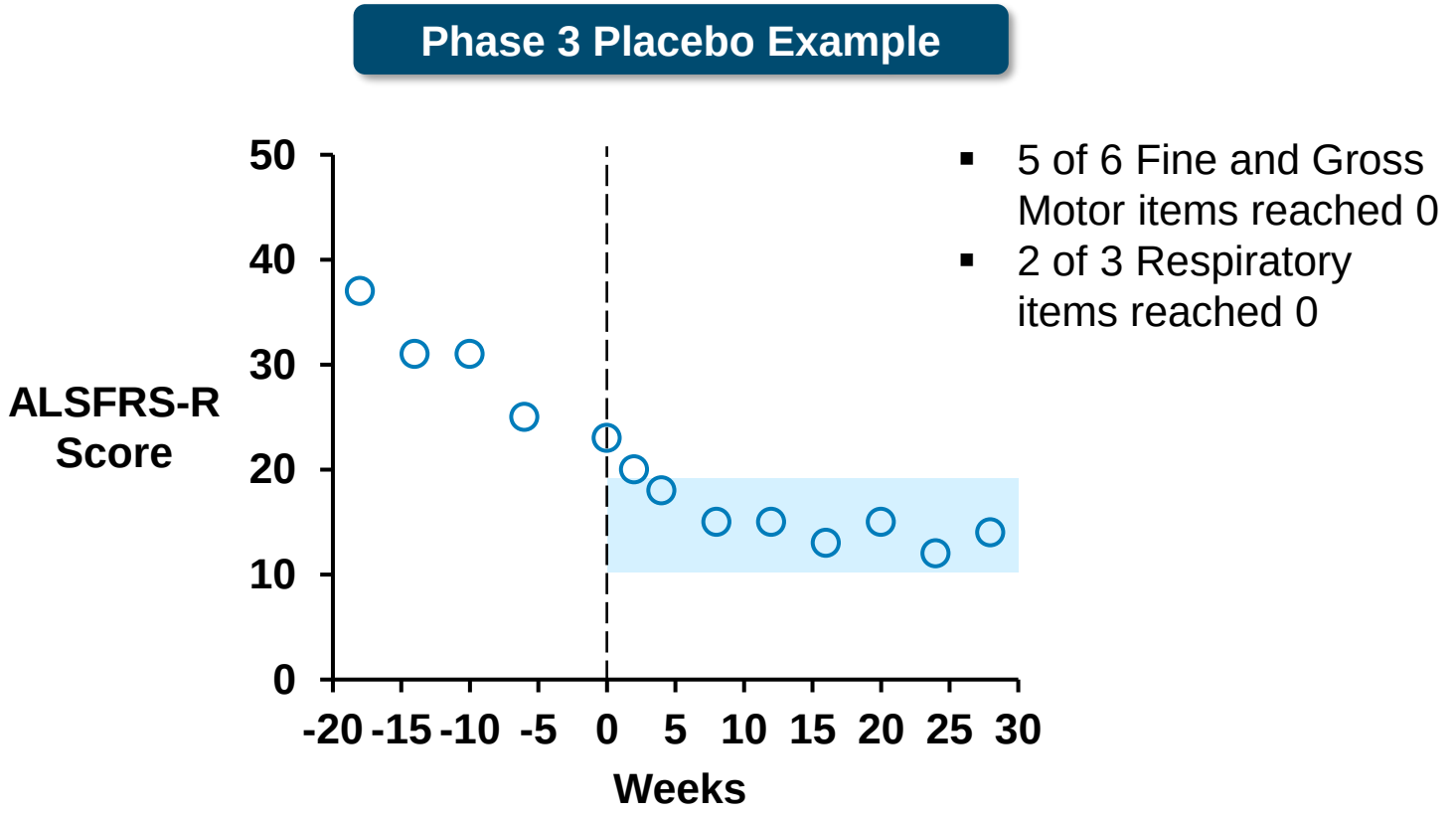
Professor and Vice Chair for Research

Department of Neurology

Mayo Clinic

Inability to Measure Further Decline Due to Floor Effect Results in Misclassification of Response

- Misclassification of response criteria (≥ 1.25 points/month reduction in decline vs pre-treatment period) can be achieved by participants due to floor effect of ALSFRS-R scale
- Suggests that participants with worst scores had clinical response

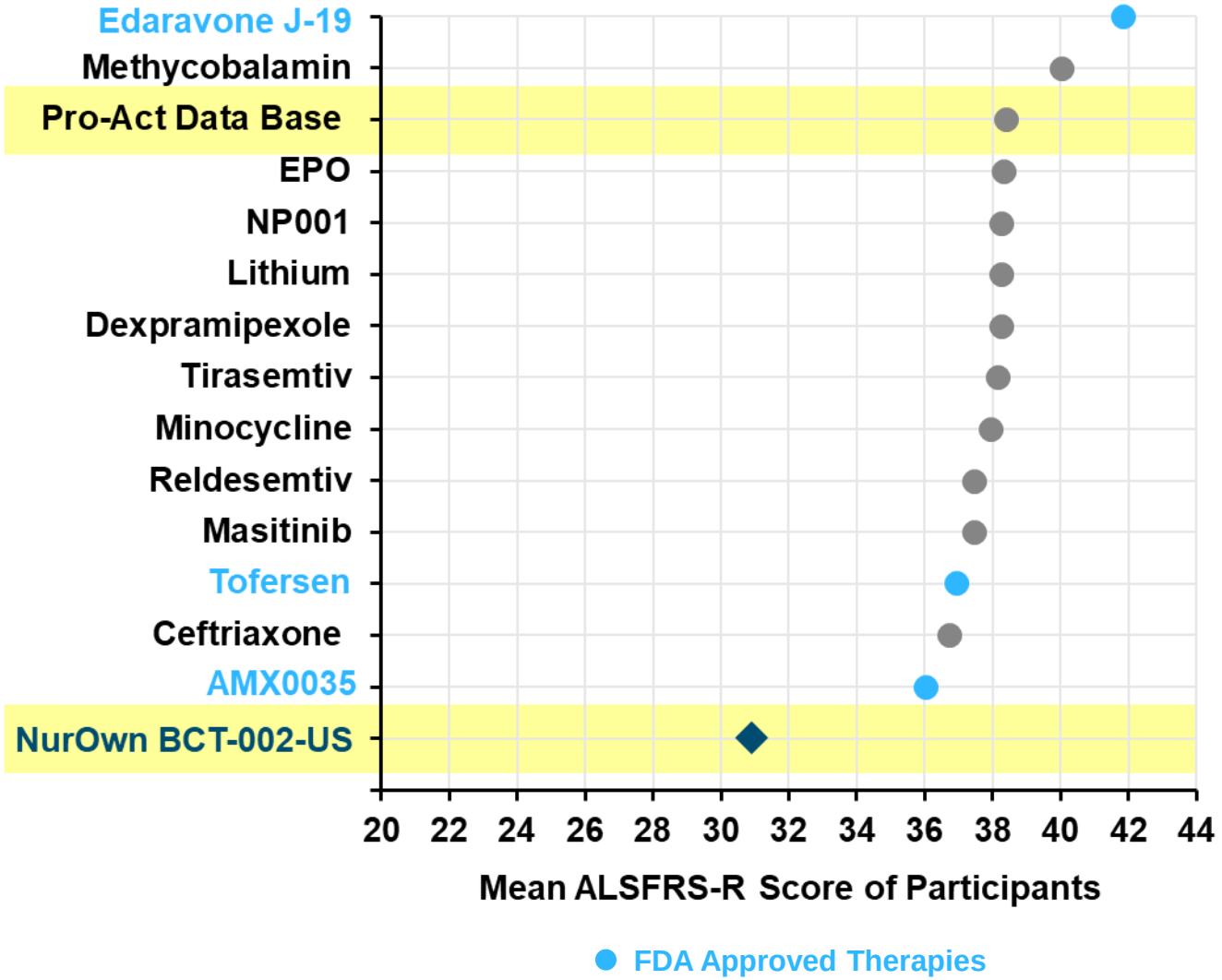


> 1/3 Participants with ALSFRS-R ≤ 25 Had Fine and Gross Motor Subscales with Items=0 at Baseline

- Participants with items=0 may continue to worsen, or plateau, within functional domain
  - Unable to measure further change due to floor effect
- 70% decline anticipated in fine and gross motor subscales

Subscales in participants with ALSFRS-R ≤ 25	% Participants with Items=0 at Baseline
Bulbar	7%
Fine Motor	42%
Gross Motor	37%
Respiratory	1%

Floor Effect Observed in Other ALS Trials

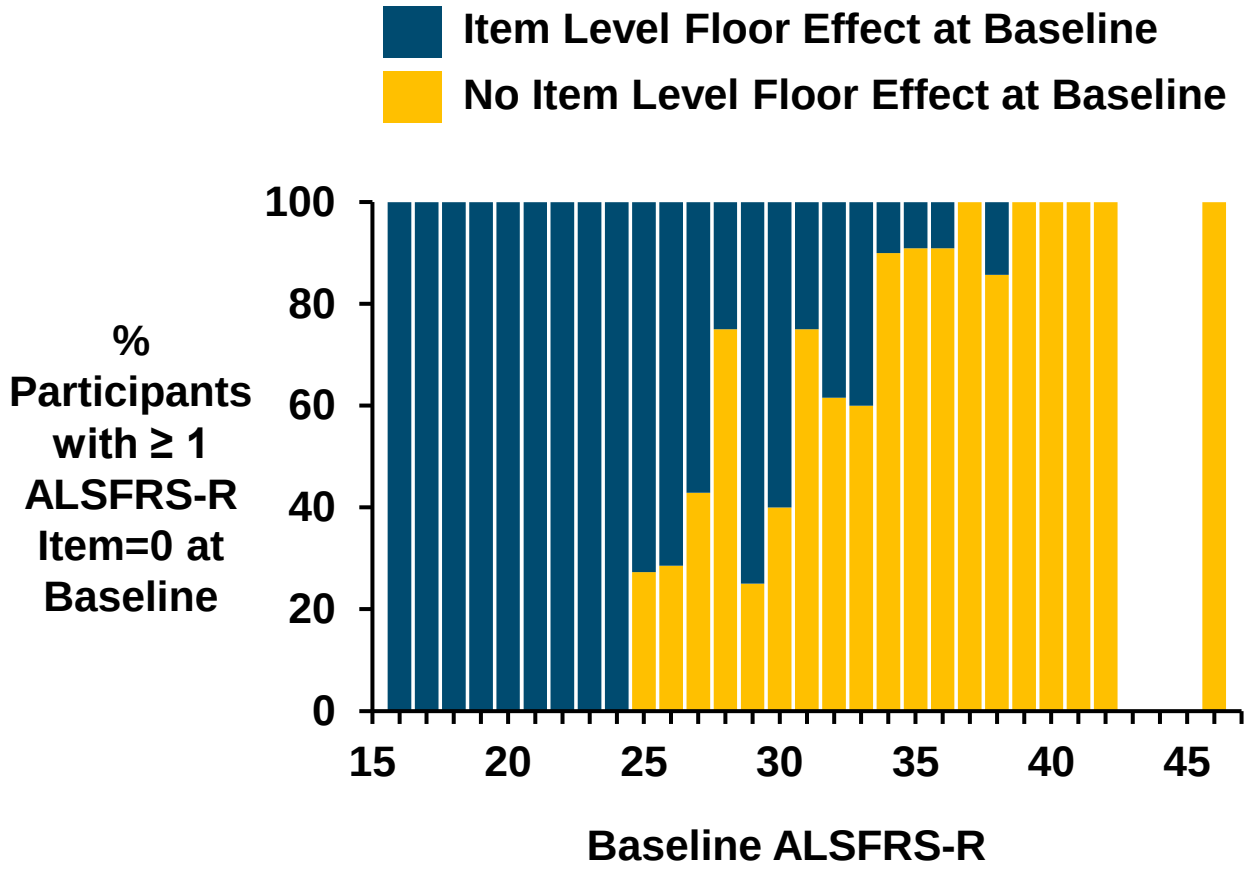


- PRO-ACT: **4.7%** of participants exhibit pattern of floor effect

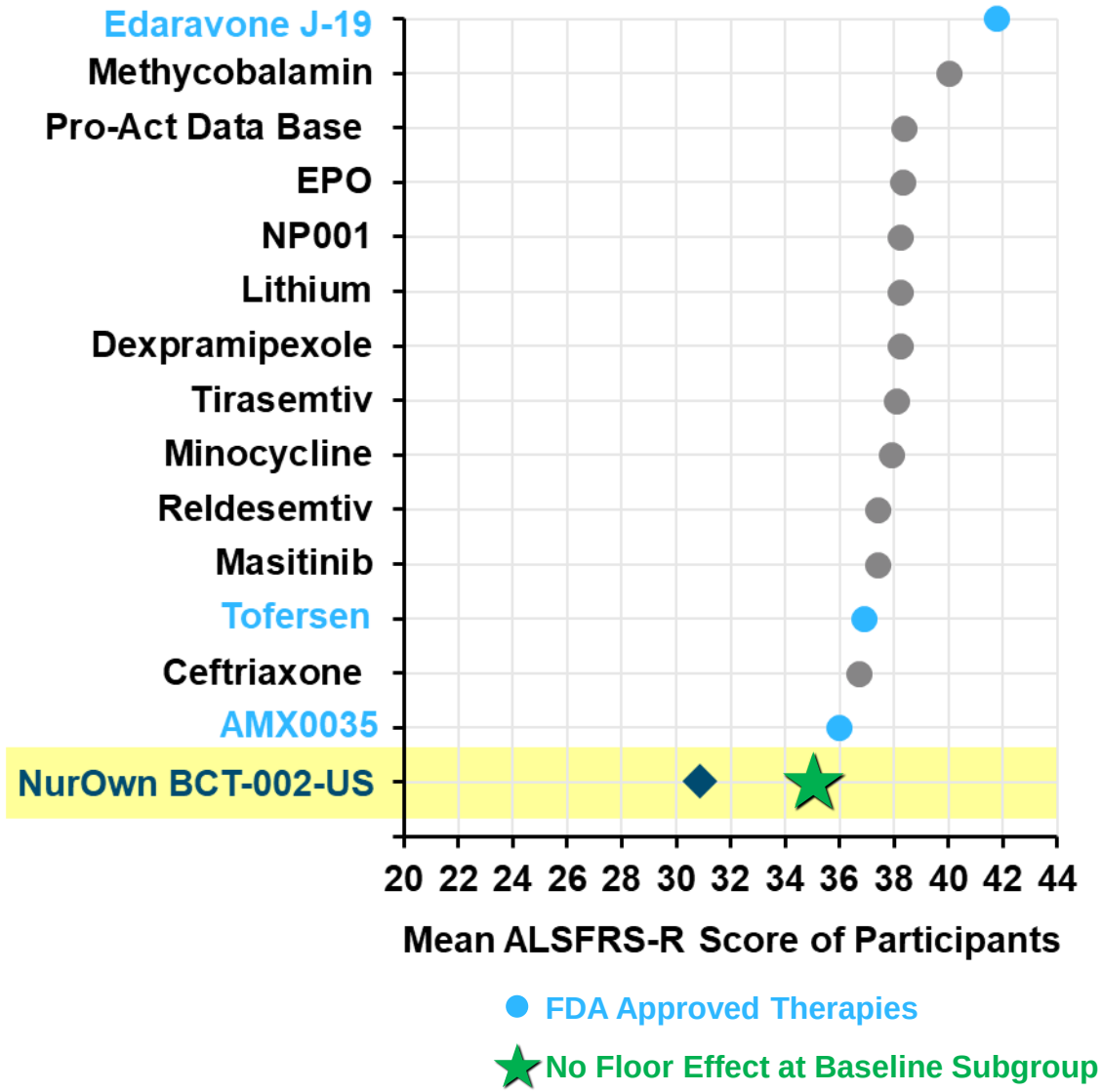
- NurOwn Phase 3: **22.3%** of placebo participants exhibit pattern of floor effect

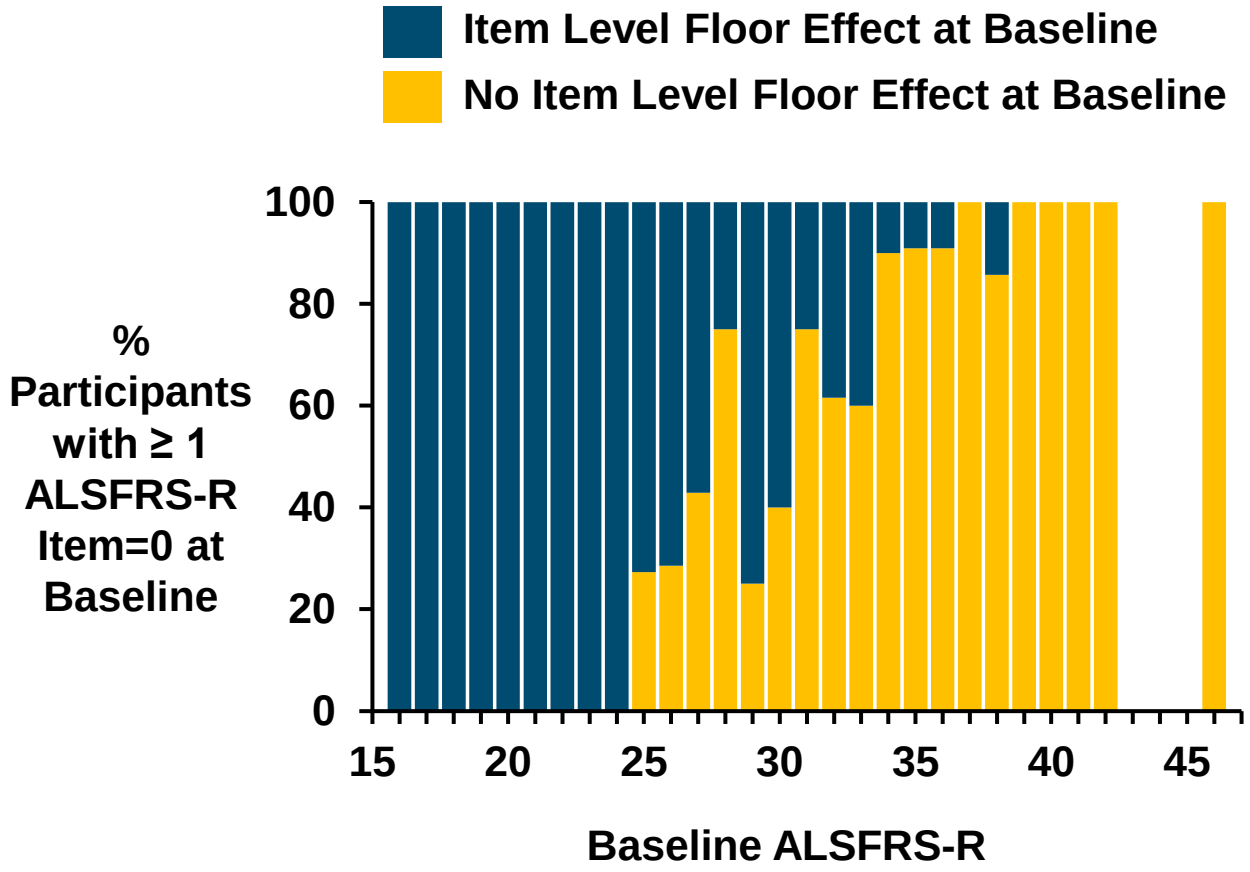
Unusually High Number of Participants Had ALSFRS-R Items=0 at Baseline

- Floor effect more prominent in participants with lower ALSFRS-R at Baseline
- 100% of participants with ALSFRS-R ≤ 24 at Baseline had ≥ 1 item=0



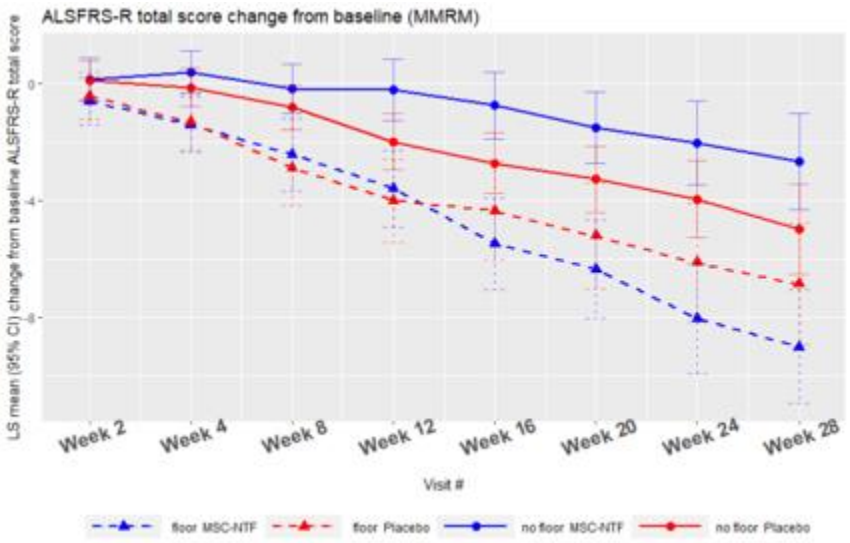
Population in NurOwn Study with No Floor Effect at Baseline Consistent with Population in Other Trials

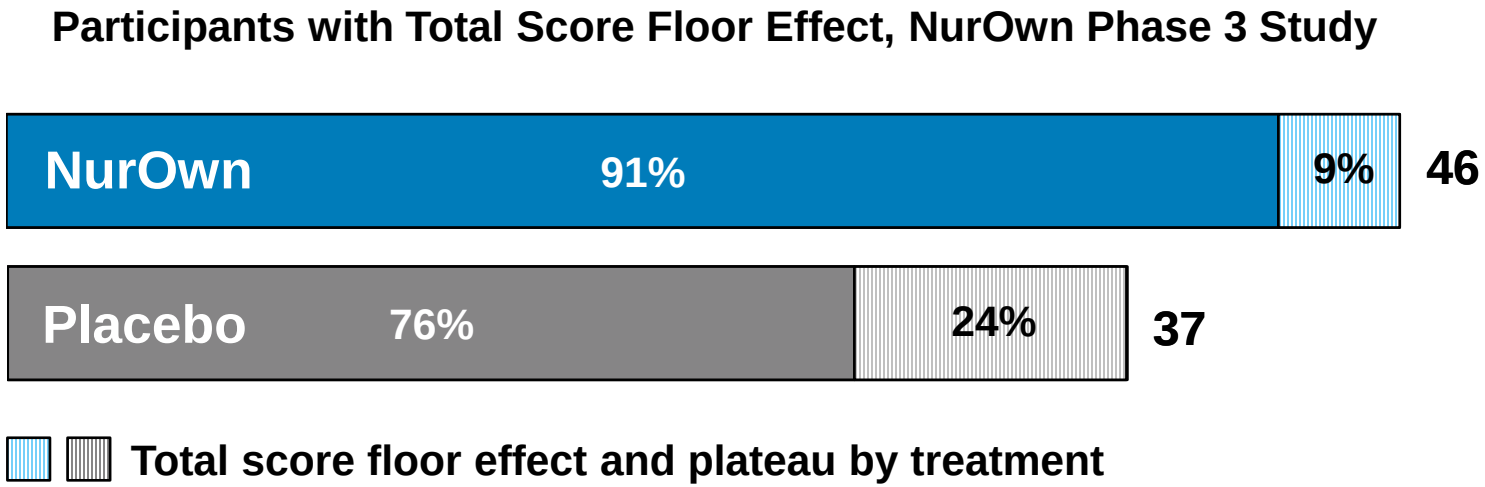




Imbalance in Floor Effect Participants in NurOwn Study

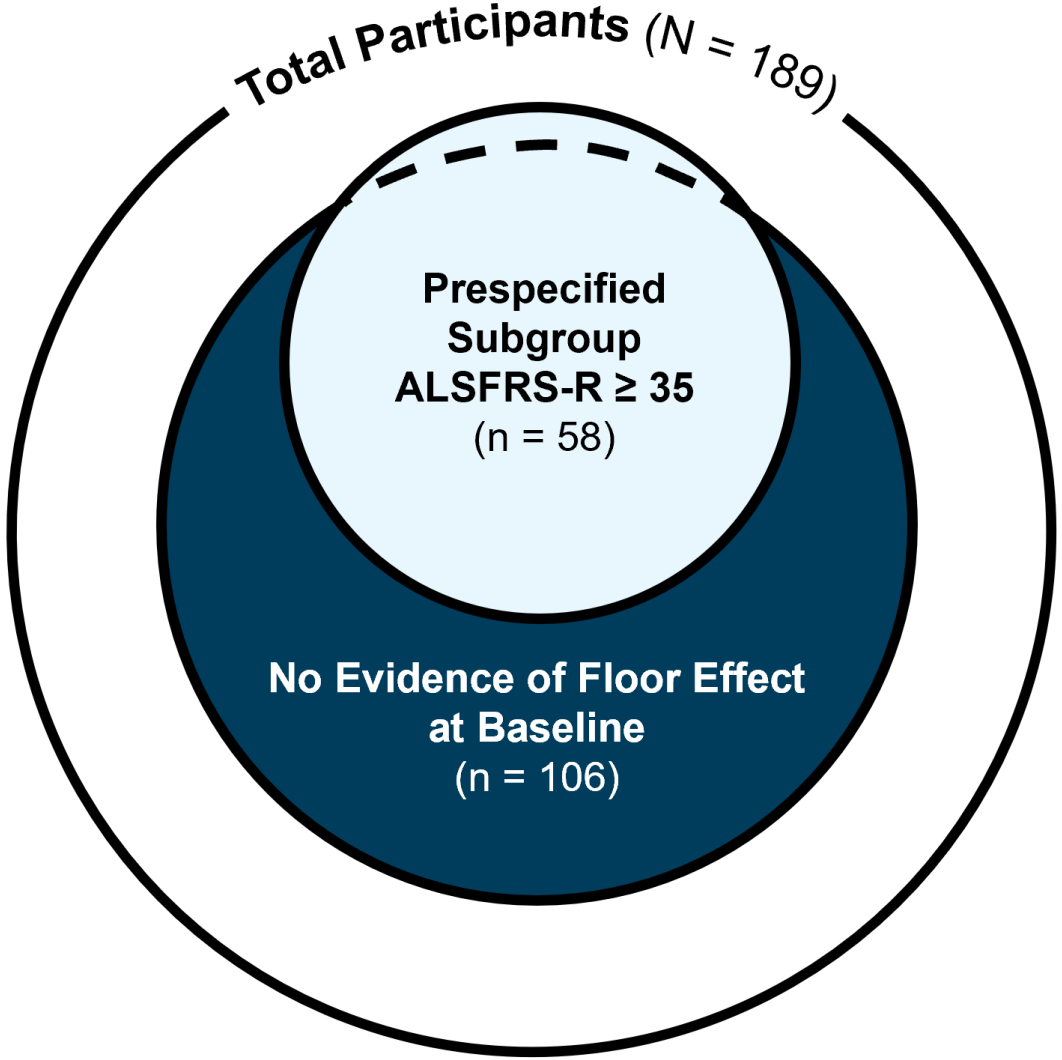
Figure 14: FDA Briefing Document



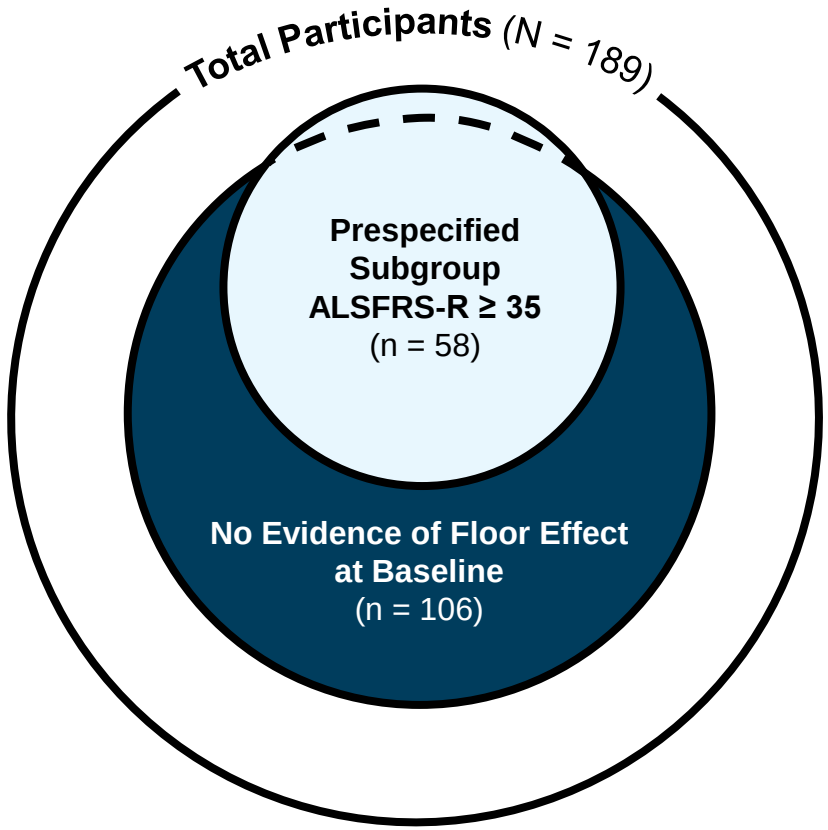


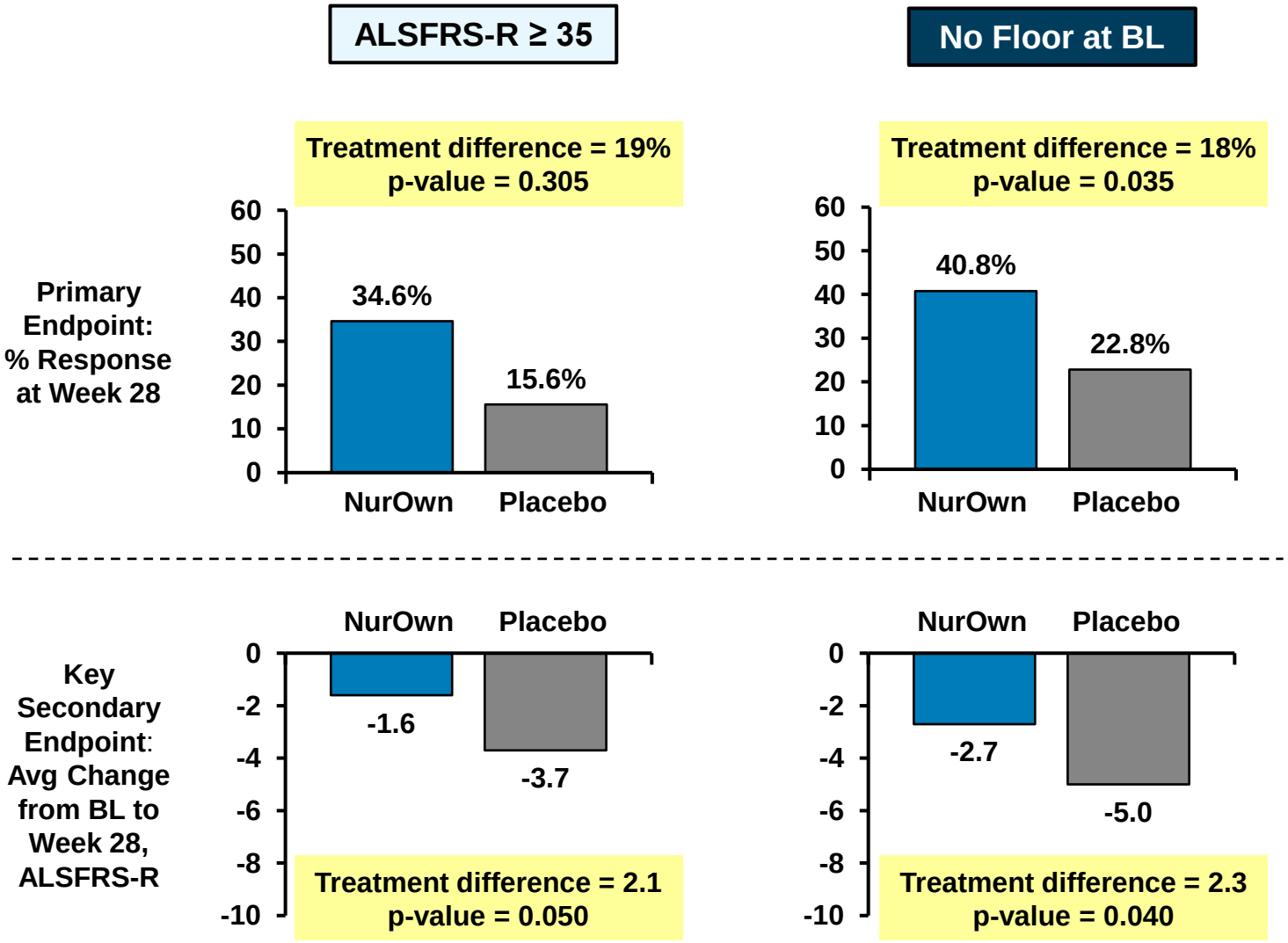
- Of participants impacted by floor effect
  - Fewer placebo participants compared to NurOwn (37 vs 46)
    - Substantially more placebo participants who plateaued on ALSFRS-R (24% vs 9%)
- Those that plateaued had lower changes from baseline in ALSFRS-R scores as scale unable to measure further decline
- Imbalance creates artifact

Supportive Evidence in Larger Subgroup with No Floor Effect



Similar Treatment Effect in Prespecified Subgroup ALSFRS-R ≥ 35 and No Floor Effect Subgroup





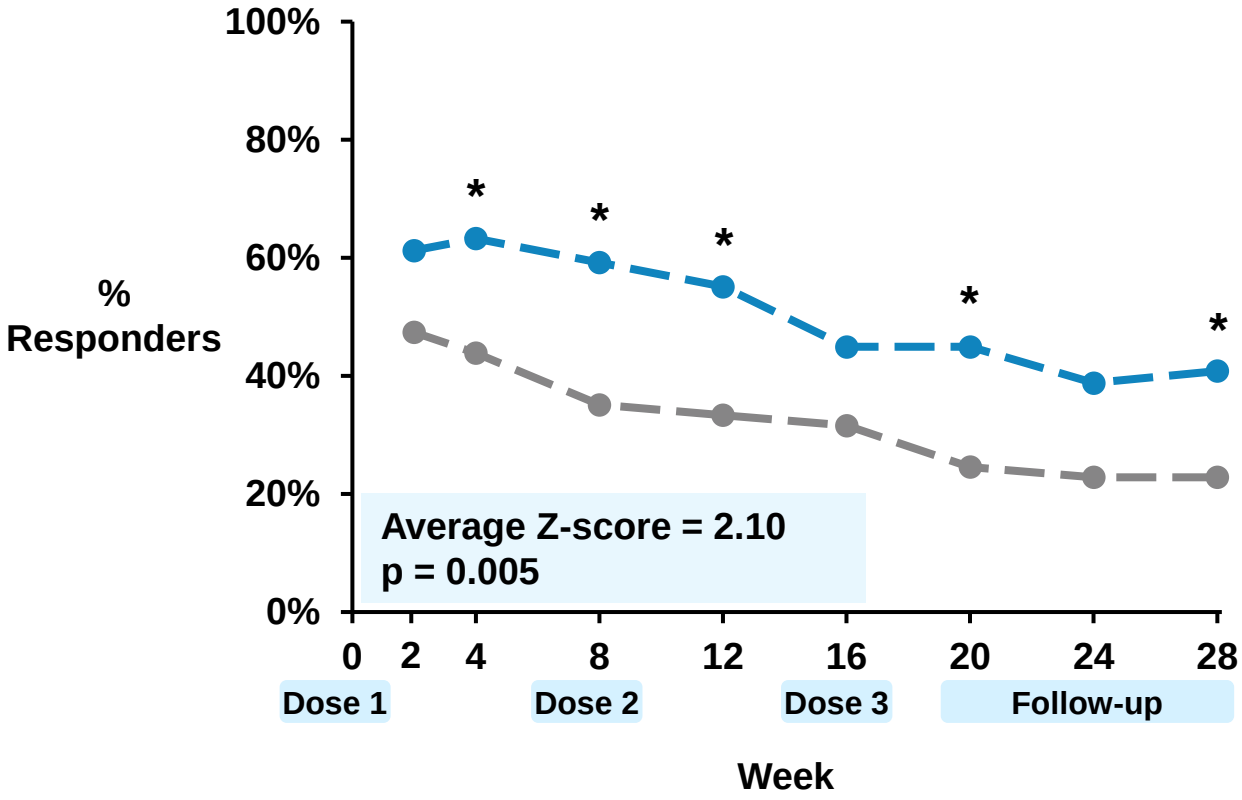
Similar Results Across Secondary Endpoints in No Floor Effect Subgroup

Secondary Endpoints	No Floor Effect		p-value
	NurOwn (N = 49)	Placebo (N = 57)	
≥ 100% improvement in ALSFRS-R slope through Week 28, n (%)	12 **(25%)**	8 **(14%)**	**0.291**
CAFS, average rank at Week 28	**91.3**	**76.7**	**0.063**
Events (Event free probability) for death due to disease progression through Week 32, n (%)	0 **(> 99%)**	1 **(98%)**	**NA***
Events (Event free probability) for death due to any cause through Week 32, n (%)	1 **(98%)**	2 **(92%)**	**0.71***

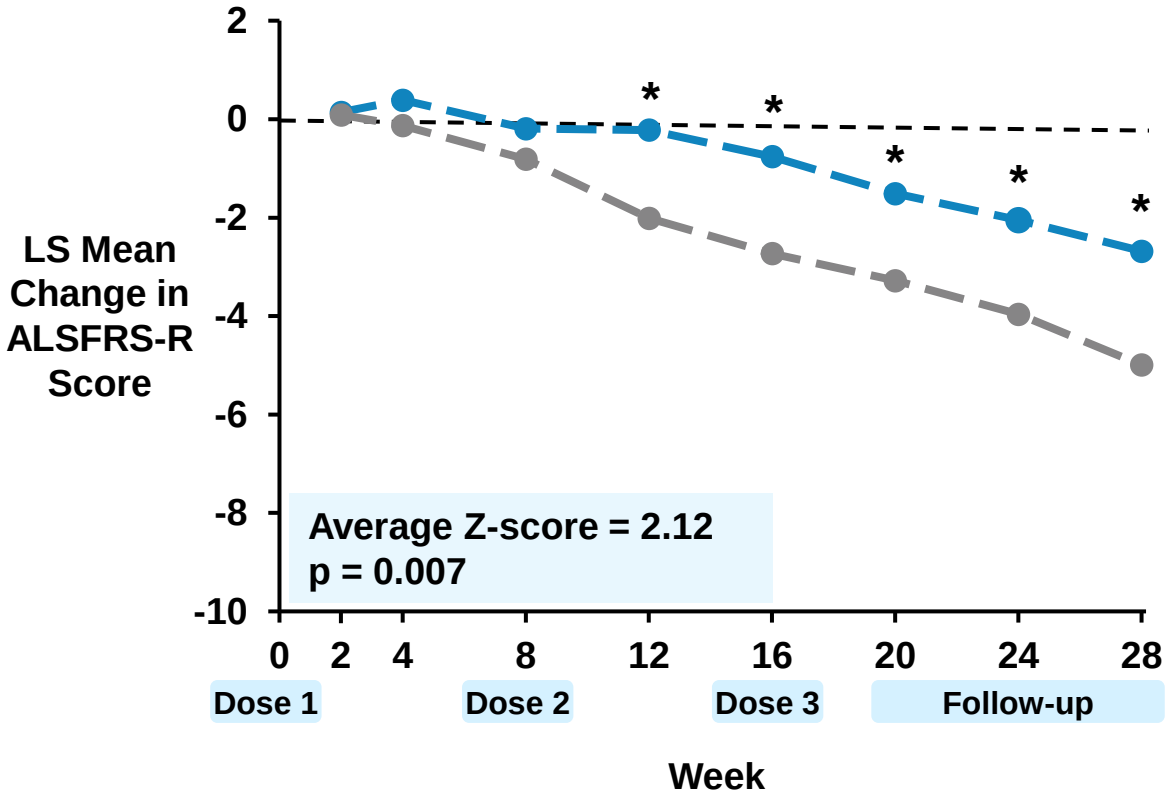
*** p-value from a prespecified Cox proportional hazards model. NA: p-value not estimable due to lack of events**

Totality of Evidence Consistent in Group with No Floor Effect on Primary and Key Secondary Endpoint

Primary Endpoint
Percent Responder



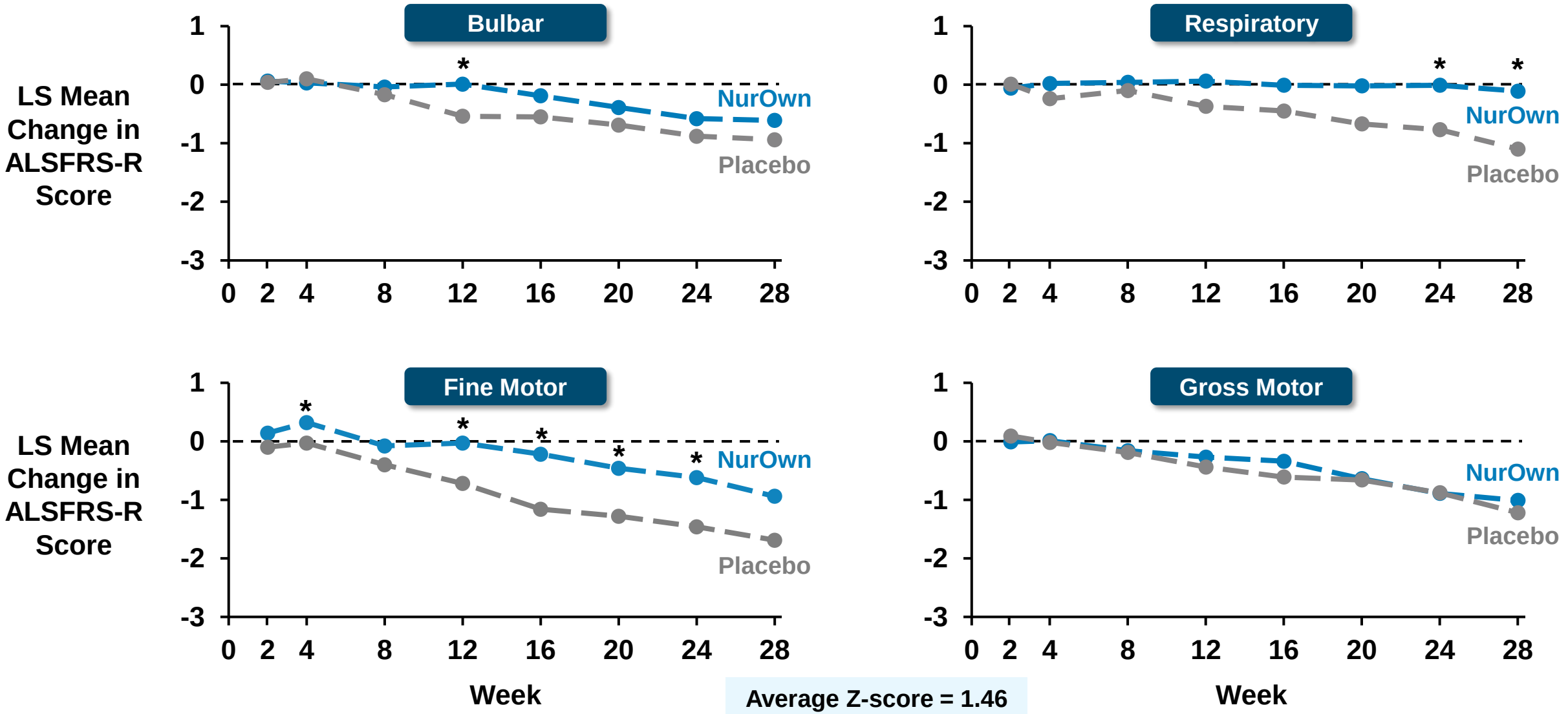
Key Secondary Endpoint
Change in ALSFRS-R Total Score



NurOwn Placebo

* p ≤ 0.05

Totality of Evidence Consistent in Participants with No Floor Effect Across ALSFRS-R Subscales



Average Z-score = 1.46
p = 0.007

* p ≤ 0.05

Floor Effect Observed in NurOwn Study Is Real and Supports Efficacy in Subgroup ALSFRS-R ≥ 35

1. Item level floor effect present in ~ half of participants; participants who plateau at a total score led to misclassification of response
2. NurOwn produced clinically meaningful and nominally significant treatment effects across primary and secondary endpoints in participants with no floor effect
3. Totality of evidence further supports validity of data; results did not occur by chance

Supportive Biomarker Results

Robert Bowser, PhD

Chief Scientific Officer, Professor, Chair

Department of Translational Neuroscience

Barrow Neurological Institute

Emerging Biomarkers Related to ALS

Neurodegeneration

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

Neuroinflammation

Pro-inflammatory

- CHI3L1 / YKL-40, Chitotriosidase-1, MCP-1, IP-10, OPG, S100B, SDF-1α, TREM-2, GFAP, IL-6, IL-8, miR-155

Anti-inflammatory

- IL-10, Fetuin-A, IL-37, TGF-β1, MSR1, miR-146a-5p, miR-146b-5p

Neuroprotection

- BDNF
- Clusterin / ApoJ
- Galectin-1
- VEGF-A
- G-CSF
- GDF-15
- HGF
- LIF
- NMNAT1
- miR-206

NfL, TGF-β1, and Galectin-1 identified by prespecified model as predicting clinical outcomes

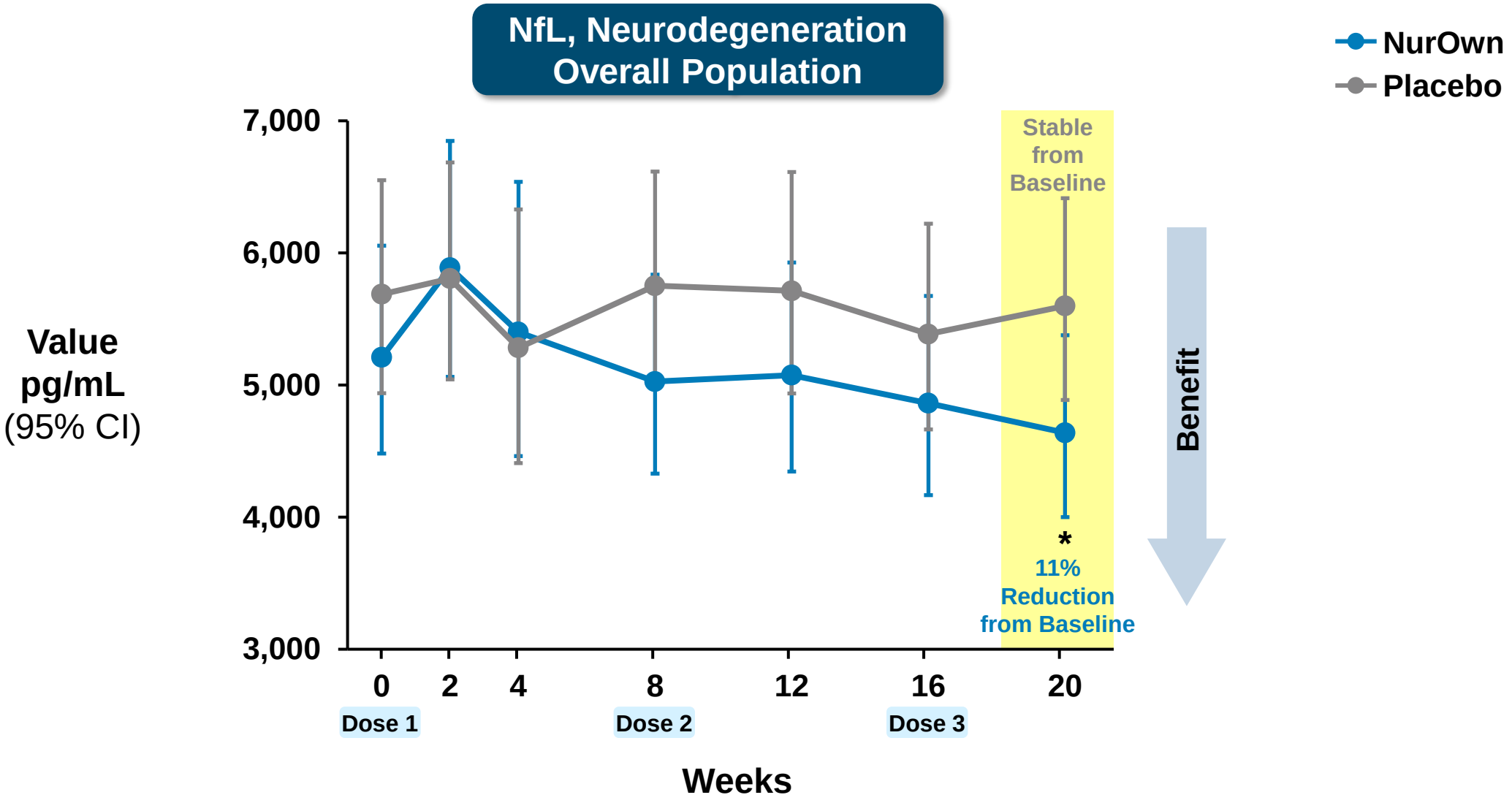
Statistically Significant Differences Between NurOwn and Placebo on Biomarkers Across 3 Primary Pathways

- CSF samples collected at 7 time points in all participants
- 33 biomarkers representing three key pathways

Primary Biomarker Pathway	Biomarkers with Overall Significant Treatment Effect	Number Markers Evaluated
Neurodegeneration	**DR6, NfL, pNfH, TWEAK**	**8**
Neuroinflammation	**MCP-1, OPG, Fetuin-A, S100B, SDF-1a, miR-146a-5p, miR-146b-5p, IL-37, MSR1, TGF-β1**	**16**
Neuroprotection	**BDNF, Clusterin/ApoJ, Galectin-1, G-CSF, GDF-15, HGF, NMNAT1, VEGF**	**9**

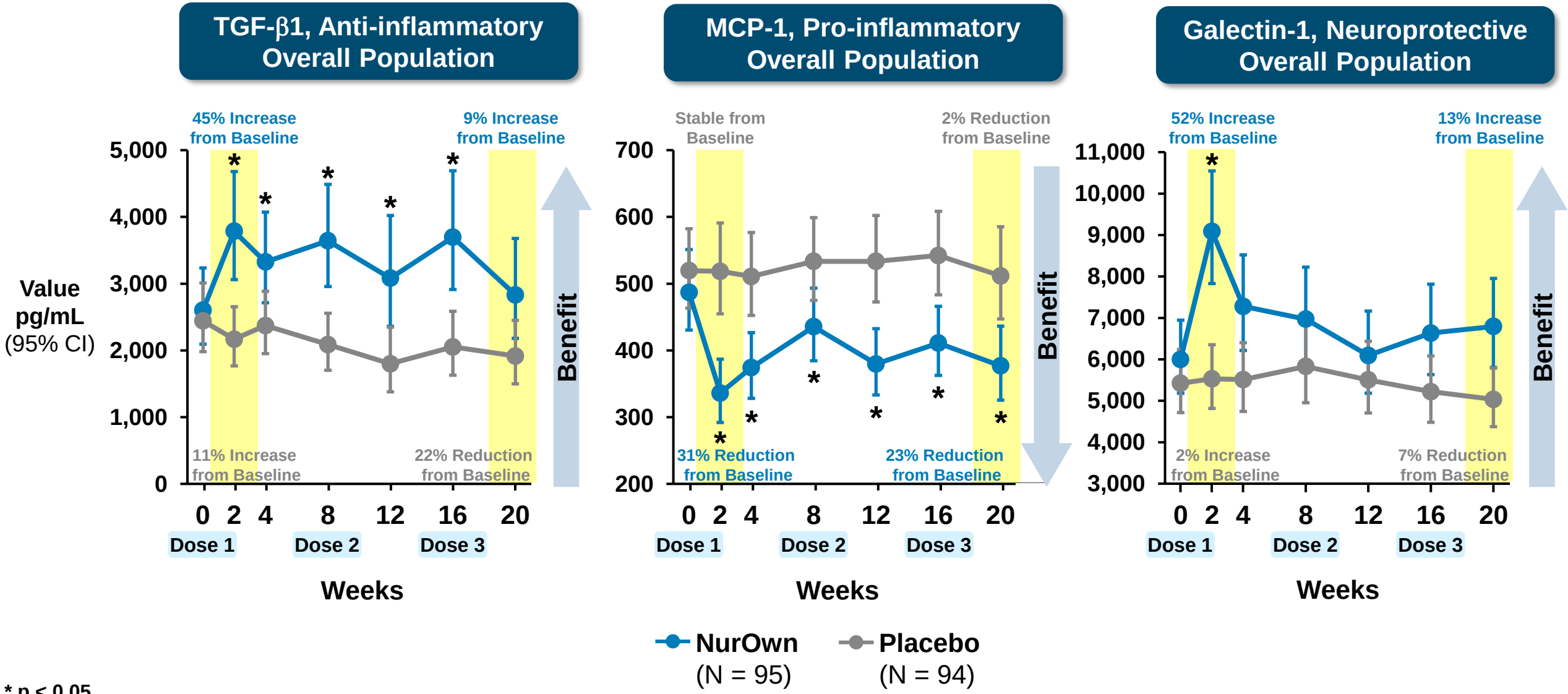
Consistent treatment effect across disease severity

NurOwn Significantly Lowers NfL Neurodegenerative Biomarker Over Time vs Placebo



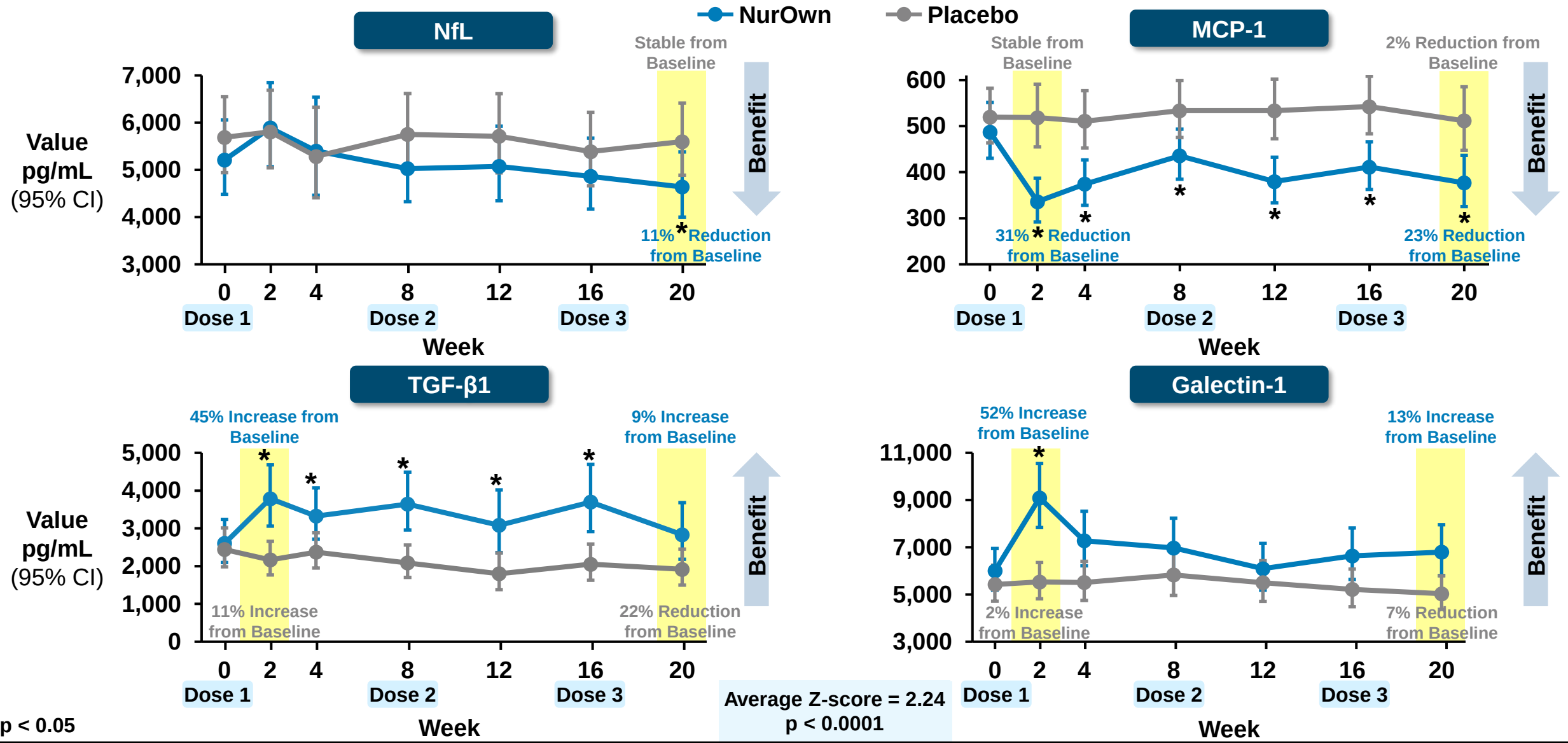
* p < 0.05

NurOwn Treatment Significantly Impacts Inflammatory and Neuroprotective Biomarkers



* p < 0.05

Totality of Evidence In All Patients Supports the MOA



* p < 0.05

NurOwn Demonstrates Evidence of Biological Effect, Biomarker Data Reinforce Clinical Outcomes

1. Significant improvements on multiple ALS biomarkers of neuroinflammation, neurodegeneration, and neuroprotection
2. Significant reduction in NfL levels from Baseline vs placebo ($p < 0.05$)
3. Totality of evidence ($p < 0.0001$) provides strong statistical evidence of NurOwn treatment effect across biomarkers longitudinally

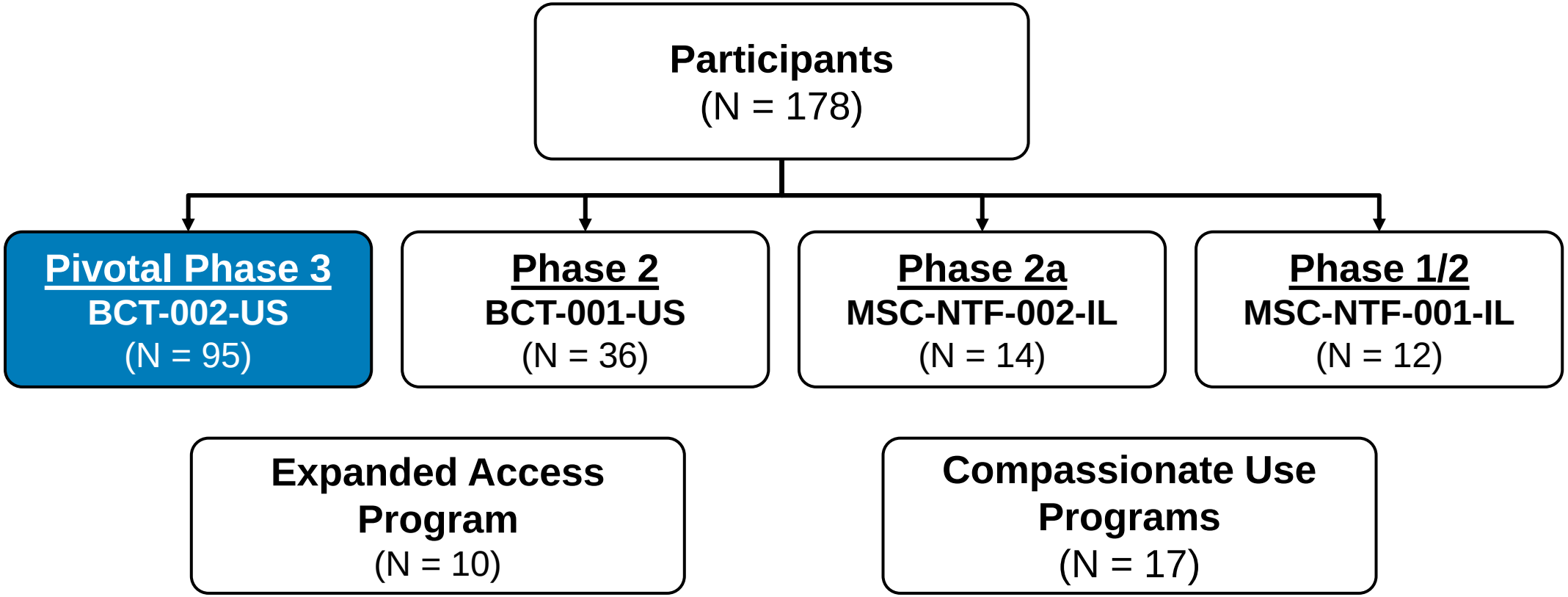
Safety

Kirk Taylor, MD

Executive Vice President and Chief Medical Officer

Brainstorm Cell Therapeutics

NurOwn Exposures Across Clinical Program



Safety Overview

Participants with ≥ 1 AE, n (%)	All Participants		ALSFRS-R ≥ 35	
	NurOwn (N = 95)	Placebo (N = 94)	NurOwn (N = 26)	Placebo (N = 32)
AE	94 **(99%)**	92 **(98%)**	25 **(96%)**	32 **(100%)**
SAE	23 **(24%)**	17 **(18%)**	1 **(4%)**	3 **(9%)**
SAE related to treatment	1 **(1%)**	1 **(1%)**	**0**	1 **(3%)**
AE leading to treatment withdrawal	1 **(1%)**	1 **(1%)**	1 **(4%)**	**0**
AE leading to study discontinuation	1 **(1%)**	3 **(3%)**	1 **(4%)**	**0**
Deaths				
Pretreatment	**0**	2 **(2%)**	**0**	**0**
On treatment	10 **(11%)**	4 **(4%)**	**0**	1 **(3%)**

Adverse Events Generally Balanced Between Treatment Groups in All Participants

Preferred Term ≥ 10% of Participants, %	NurOwn (N = 95)	Placebo (N = 94)
Participants with ≥ 1 AE	**99%**	**98%**
Procedural pain	53%	36%
Headache	47%	34%
Back pain	44%	26%
Procedural headache	33%	32%
Fall	31%	36%
Post lumbar puncture syndrome	23%	31%
Nausea	17%	19%
Pain in extremity	17%	12%
Post procedural complication	17%	7%
Musculoskeletal pain	16%	9%
Muscular weakness	12%	13%
Dysphagia	12%	7%
Coccydynia	12%	1%
Arthralgia	11%	7%
Laceration	7%	12%
Upper respiratory tract infection	6%	13%

SAEs Consistent with ALS Disease Progression in All Participants

Preferred Term (SAE > 1 Participant in Either Treatment Group), n (%)	NurOwn (N = 95)	Placebo (N = 94)
Participants with ≥ 1 SAE	23 **(24%)**	17 **(18%)**
Respiratory failure[1]	5 **(5%)**	3 **(3%)**
Dysphagia	3 **(3%)**	2 **(2%)**
Pneumonia	2 **(2%)**	2 **(2%)**
Respiratory distress[1]	2 **(2%)**	**0**
Venous thromboembolism (deep vein thrombosis, pulmonary embolism)	1 **(1%)**	3 **(3%)**
Disease progression	1 **(1%)**	2 **(2%)**

1. Respiratory failure and distress captured as fatal SAEs, following participants' hospice care and DNR wishes in place

Overview of Deaths in All Participants

Deaths, n	Cause of Death	Date of Death	Baseline ALSFRS-R	Last Visit ALSFRS-R
NurOwn				
8	ALS progression	Wk 15.9	16	11
		Wk 26.3	17	10
		Wk 7.6	19	19
		Wk 13.6	21	10
		Wk 21.6	24	14
		Wk 14.9	25	18
		Wk 27.6	26	9
		Wk 25.1	29	11
1	Saddle embolism of pulmonary artery	Wk 10.7	30	27
1	Voluntary euthanasia	Wk 20.4	32	29
Placebo				
3	ALS progression	Wk 10	20	7
		Wk 24.4	32	25
		Wk 29.3	25	15
1	Cardiac arrest from accident	Wk 28.7	36	35
1*	ALS progression	Pre-treatment	14	13
1*	Cardiac arrest	Pre-treatment	22**	22**

* Patient died before receiving treatment; ** Values missing, closest available pre-treatment value used

NurOwn Not Expected to Have Any DDIs

- Formal drug-drug interaction studies not conducted
- NurOwn cells are participants' own cells
  - No risk of rejection
  - No need for immunosuppressive agents, which can cause severe and/or long-term side effects

Safety Conclusion

1. NurOwn well tolerated with manageable AEs; most events mild or moderate in severity
2. Deaths mainly caused by disease progression and most had advanced disease at Baseline
3. Favorable safety profile in prespecified subgroup ALSFRS-R ≥ 35;
   1 SAE and no death reported on NurOwn

Clinical Perspective

Anthony J. Windebank, MD

Professor of Neurology

Judith and Jean Pape Adams Professor of Neuroscience

Mayo Clinic

FDA Regulatory Flexibility in ALS

- Riluzole: post hoc analyses showed a moderate increase in survival
- Edaravone: 3 failed Phase 3 trials; followed by one study showing less decline in function on ALSFRS-R
- RELYVRIO: Phase 2 trial; post-hoc analyses suggesting longer median overall survival
- QALSODY (Tofersen): failed Phase 3 trial; accelerated approval based on post-hoc analysis of NfL biomarker data

We All Want Safe and Effective Therapies for Patients

- Safe and effective rarely means cure
- ALS is where cancer was 40 years ago
  - Incredible advances in cancer treatments built on many incremental study effects
- Need to build on ALS research and incremental results

Cannot afford to lose a potentially valuable treatment simply because of complex data

NurOwn Efficacy and Safety Data Support Approval

- Compelling and clinically meaningful results in prespecified subgroup ALSFRS-R ≥ 35
- Results consistent across multiple analyses accounting for floor effect
- Biomarker data on neurodegeneration, neuroinflammation, and neuroprotection reinforce clinical outcomes
- Acceptable safety profile
- Procedure well tolerated

Examples of Improvements in Daily Activities

- “Walking without a walker”
- “Climb up and down stairs
- “Use the bathroom and showering unassisted”
- “Holding a pen to write”
- “Speaking more clearly without needing a caregiver to translate”
- “Breathing stronger”

Want to see NurOwn available for people living with ALS

NurOwn® for Treatment of ALS

September 27, 2023

Cellular, Tissue, and Gene Therapies Advisory Committee

Brainstorm Cell Therapeutics