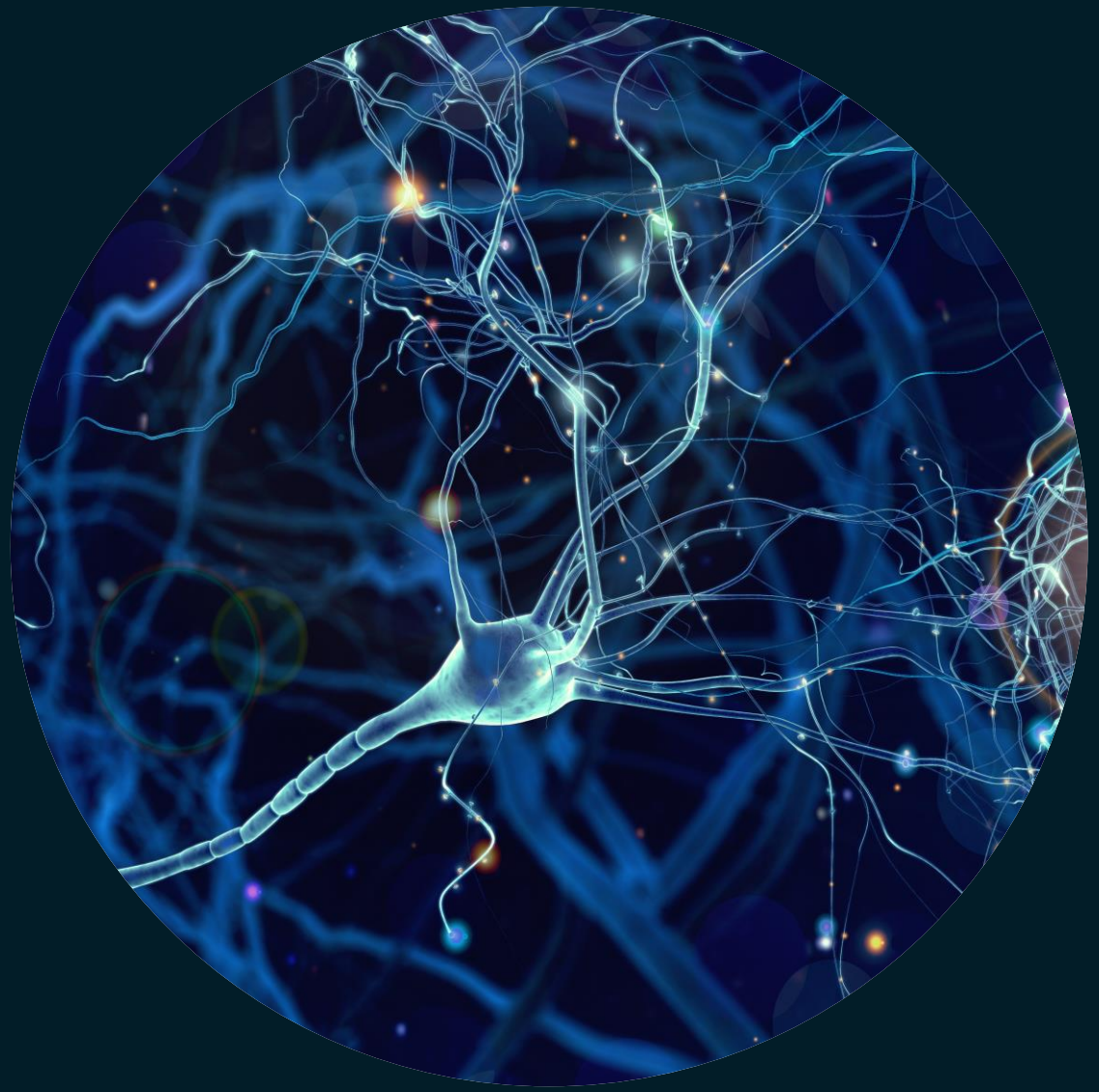

ALS Baseline Characteristics and Efficacy Outcomes in the NurOwn Phase 3 ALS Clinical Trial

Cudkowicz M, Brown R, Windebank A, Goyal N, Berry J, Miller R, Burford M, Staff N, Katz J, Kern R, Gothelf Y, Lebovits C, Lindborg S

2021 ALS One Research Symposium
November 30, 2021

Disclosures

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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

Robert Brown: Reports personal fees from Wave Lifesciences and serves on advisory boards of ALS Finding a Cure, Project ALS, and NEALS

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

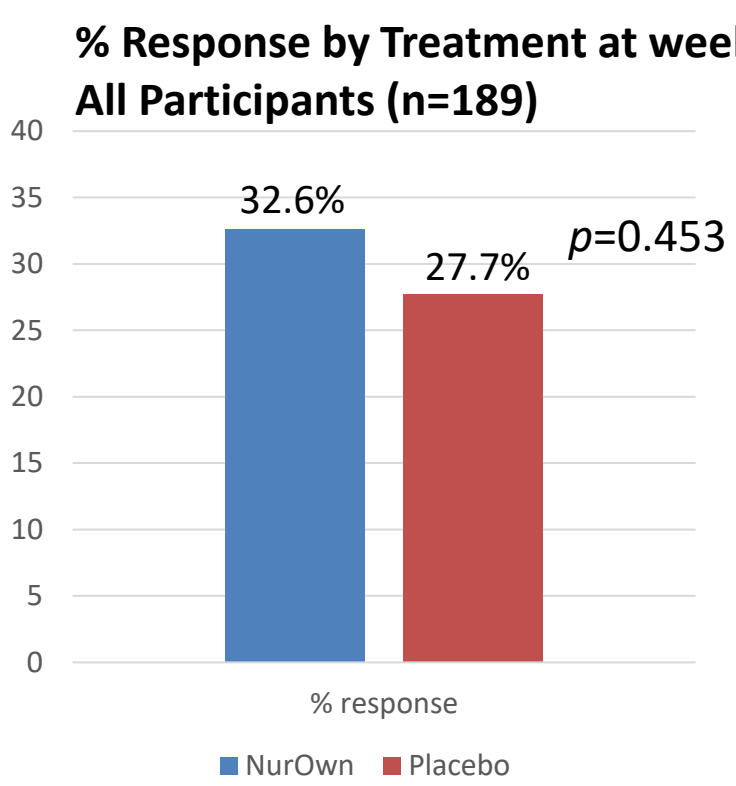
Jonathan Katz: reports consulting fees from MT Pharma, Denali Therapeutics, Biogen, Genetech, Amylyx, Cytokinetics, Wave, and Calico

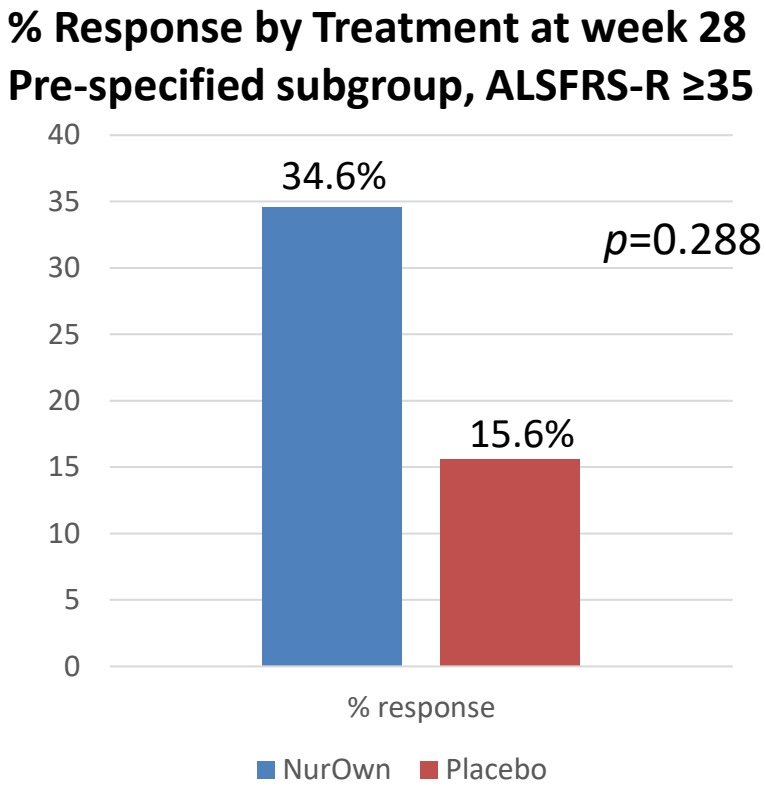
Anthony Windebank, Robert Miller, Matthew Burford: have no conflicts of interest to report

Ralph Kern, Yael Gothelf, Chaim Lebovits, Stacy Lindborg: are employed by Brainstorm Cell Therapeutics

Responder Analysis, Improvement in Rate of Decline in ALSFRS-R

Primary Endpoint Analysis at Week 28, fails to reach statistical significance in overall study

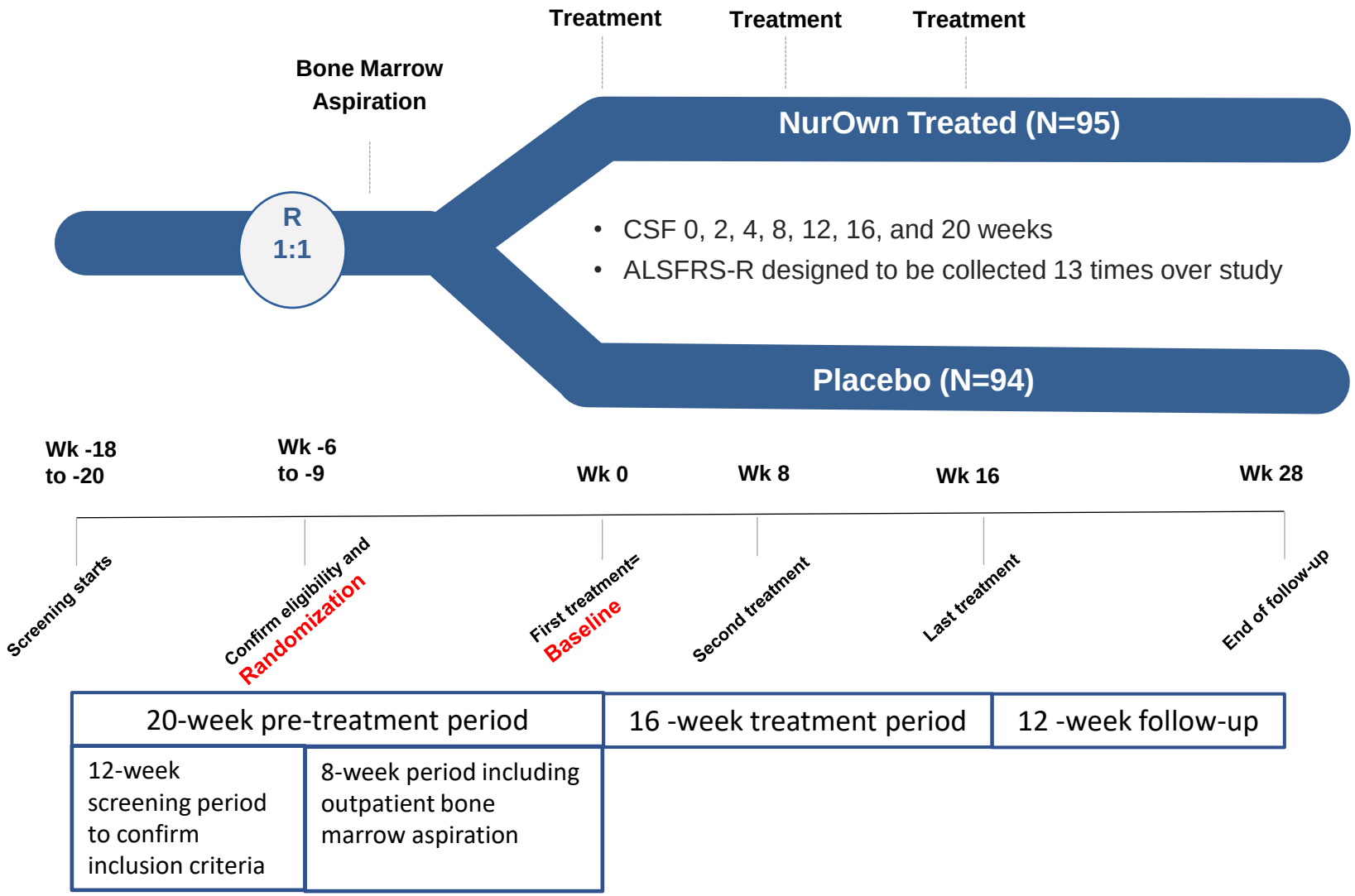




Pre-specified and post-hoc analyses suggest a potential treatment effect with MSC-NTF across primary and secondary efficacy endpoints

Phase 3 Trial of NurOwn® in ALS Patients : Protocol

Double-blind, Placebo-controlled, Randomized Trial



ClinicalTrials.gov Identifier: NCT03280056

Phase 3 Trial of NurOwn® in ALS Patients : Inclusion Criteria

Double-blind, Placebo-controlled, Randomized Trial

Key Inclusion Criteria:

- 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*
- Onset of ALS disease symptoms, including limb weakness within 24 months at the Screening Visit
- Upright slow vital capacity (SVC) measure ≥ 65% of predicted for gender, height, and age at the screening Visit

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

Phase 3 Trial of NurOwn® in ALS Patients : Endpoints

Double-blind, Placebo-controlled, Randomized Trial

Primary Endpoint

A responder analysis of the 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 Wk28

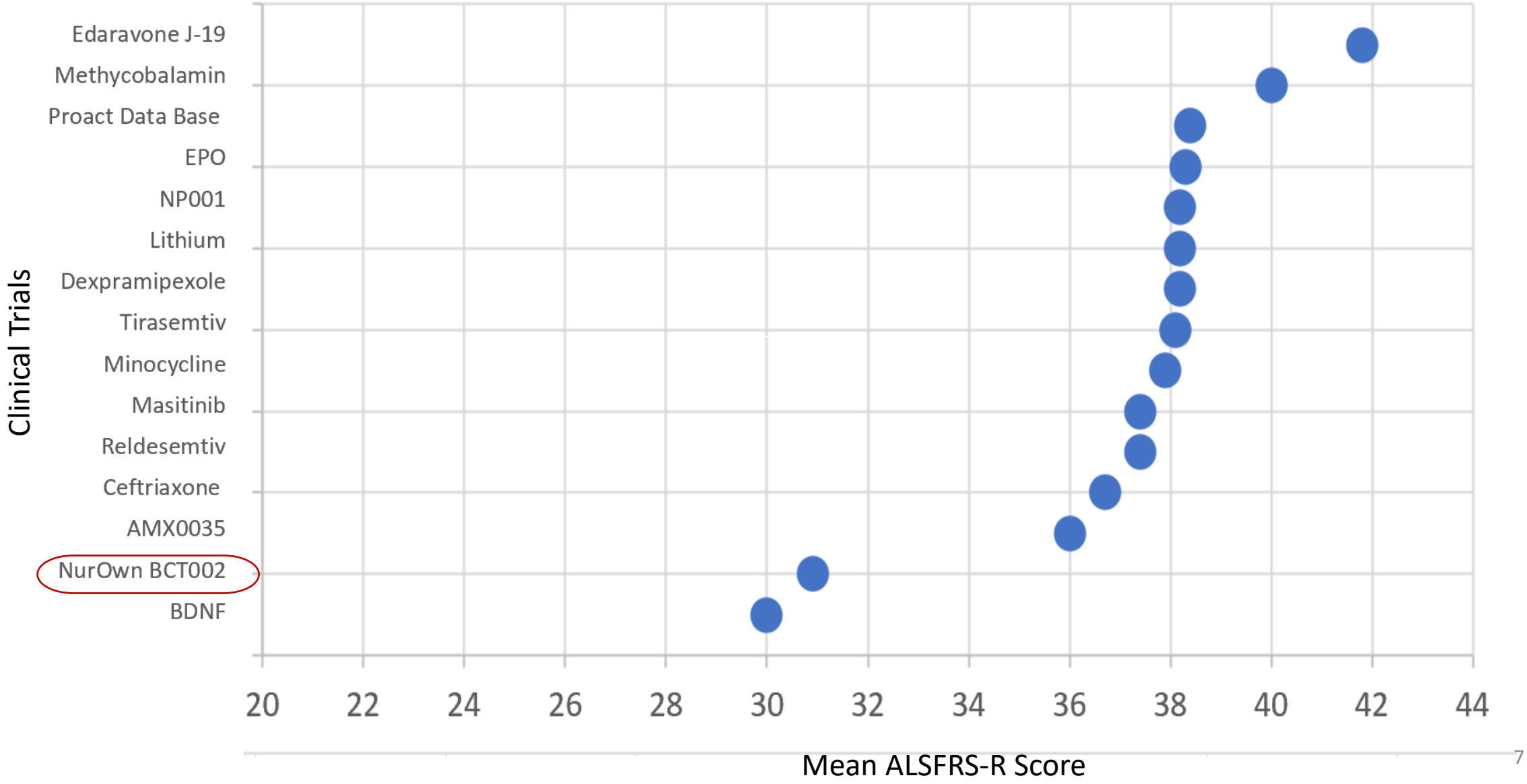
Secondary Endpoints

- Safety
- ALSFRS-R change from baseline
- Combined Analysis of Function and Survival
- Slow Vital Capacity
- CSF/Blood biomarkers

ClinicalTrials.gov Identifier: NCT03280056

BCT-002 had a unique range of ALS Disease severity (severe ALS)

Mean Baseline ALSFRS-R Score in Phase 2 & 3 Clinical Trials

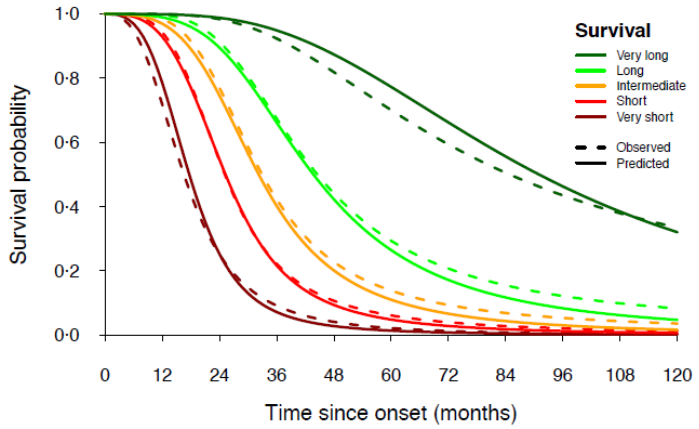


ENCALS: Personalized Prognosis in ALS

Time to survival free of non-invasive ventilation ≥ 23 hours/day, tracheostomy or death

- Rigorous model development, published 2019 in Lancet
- 11,475 ALS patients from 14 European ALS centres across 9 countries participated.
- Total follow-up was 40,016 years and median follow-up time of 97.5 months.
- Model designed to identify 5 categories of Prognosis trajectories
- Backward elimination methodology was used to select 8 terms out of 16 candidate predictors for the multivariate prediction model

Terms in the final model:
Age of onset, FVC, Diagnostic delay, ALSFRS-R slope, Bulbar onset, 'Definite' ALS,
Presence of FTD or C9org repeat expansion

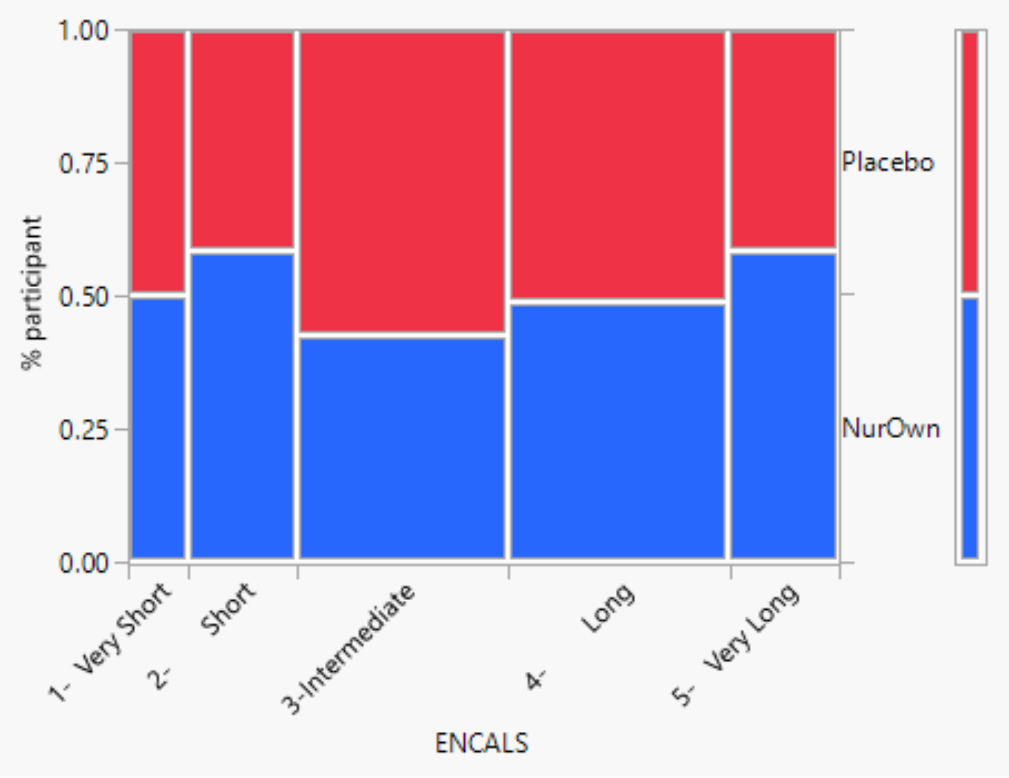


ALS centres: University Medical Centre Utrecht, The Netherlands; Trinity College, Ireland; University of Torino, Italy; Kings College, UK; University of Sheffield, UK; University of Oxford, UK; University of Lisbon, Portugal; Hannover Medical School, Germany; Kantonsspital St. Gallen, Switzerland; CHU det Tours, CHU de Limoges, France; University of Leuven, Belgium; Beaumont Hospital, Ireland

ENCALS model: NurOwn's Phase 3 trial enrolled a broad set of patients

NurOwn and Placebo treatment groups had patients across all 5 ENCALS categories

ENCALS model prediction,
Baseline distribution

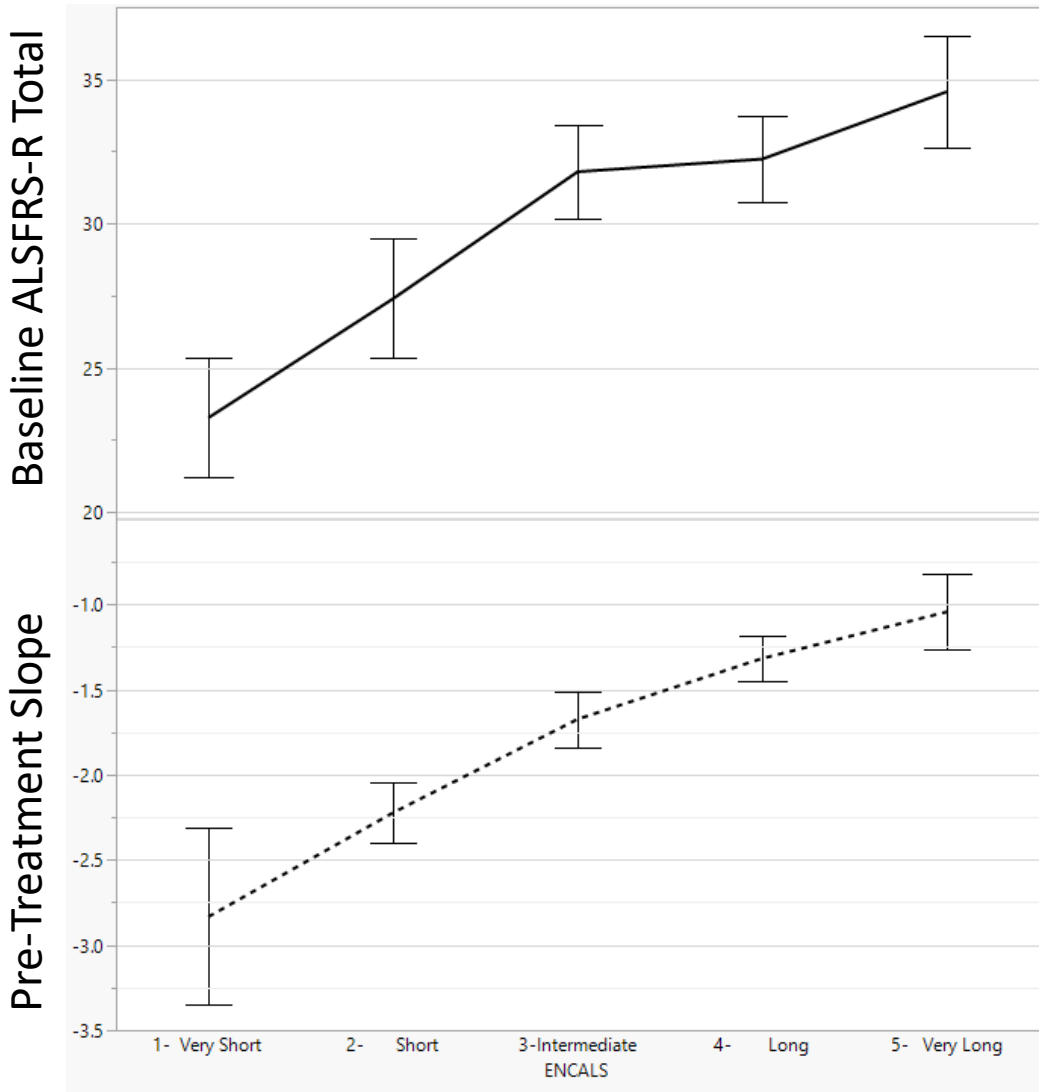


BCT-002 prediction via ENCALS model	NurOwn	Placebo	Total
Very short	8 (4.2%)	8 (4.2%)	16 (8.5%)
Short	17 (9.0%)	12 (6.3%)	29 (15.3%)
Intermediate	24 (12.7%)	32 (16.9%)	56 (29.6%)
Long	29 (15.3%)	30 (15.9%)	59 (31.2%)
Very Long	17 (9.0%)	12 (6.4%)	29 (15.3%)
Total	95 (50.3%)	94 (49.7%)	189

ENCALS categories and Baseline ALSFRS-R, Pre-treatment Slope

Participants predicated to have the shortest survival have larger pre-treatment slopes and lower baseline ALSFRS-R scores

Mean and 95% Confidence Interval, all participants

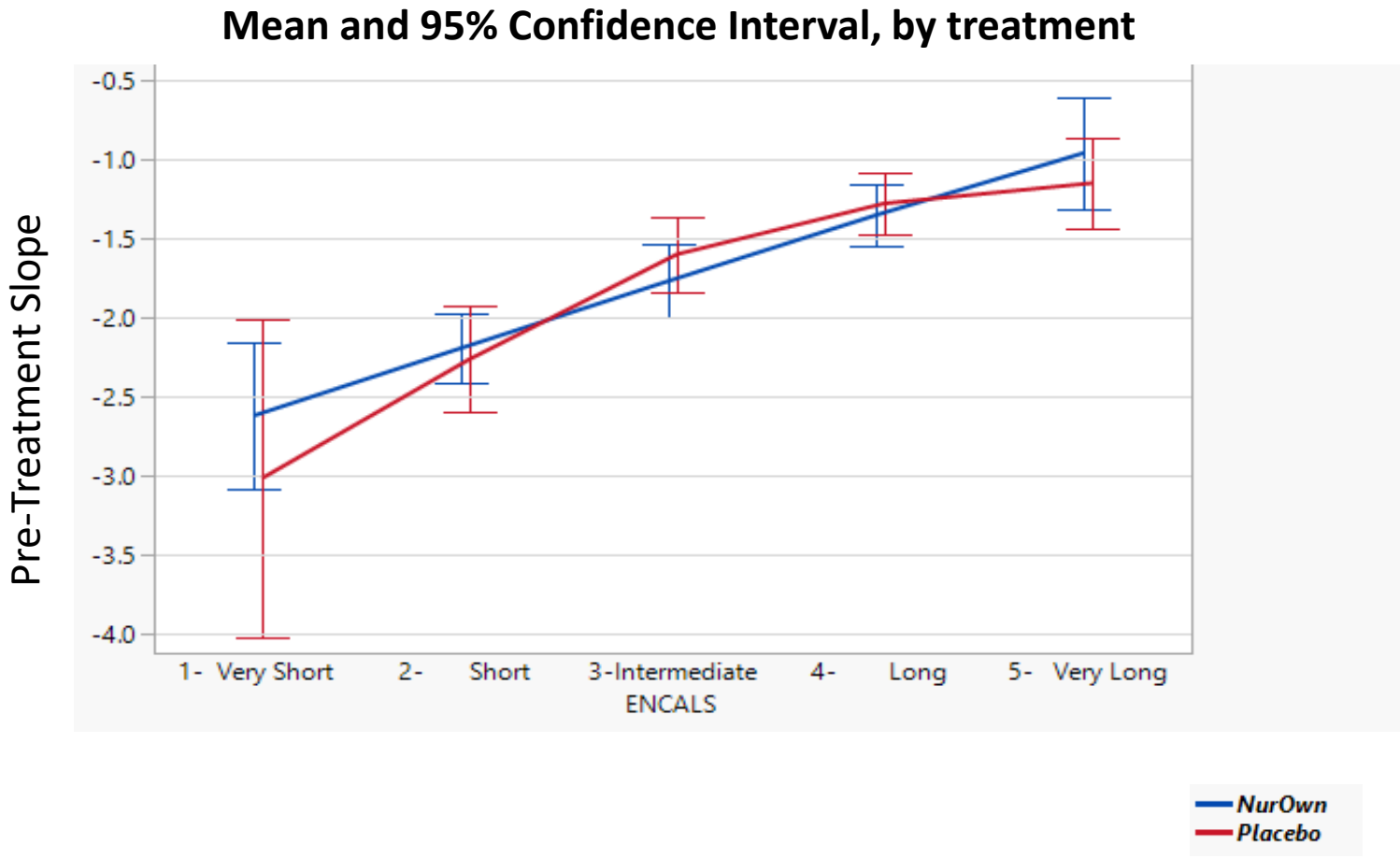


Observations:

- Participants predicted by ENCALS to have shorter survival have larger pre-treatment slopes and lower baseline ALSFRS-R values
- Statistical analysis suggests that the pre-treatment slope is more relevant in determining the ENCALS prediction category
- There is more variability in the pre-treatment slope in the in the “very short” compared to other ENCALS categories

Relationship between ENCALS categories and Pre-treatment Slope

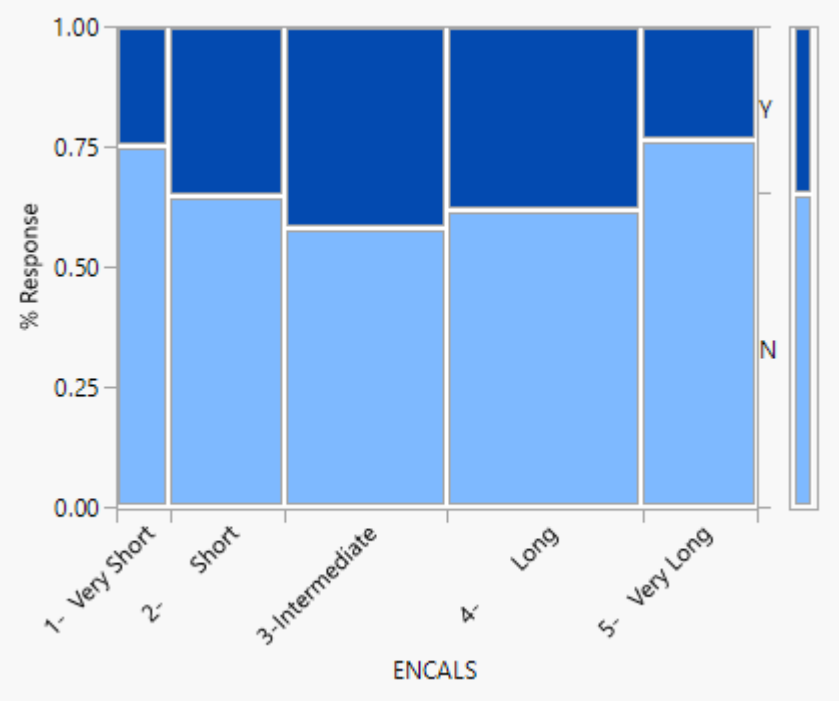
There are more Placebo participants with larger pre-treatment slopes of those predicted by ENCALS to survive "Very Short"



Phase 3, Primary Endpoint analyzed using ENCALS model

Inclusion of participants with severe ALS may have had a dilution effect, reducing the ability to show a treatment effect

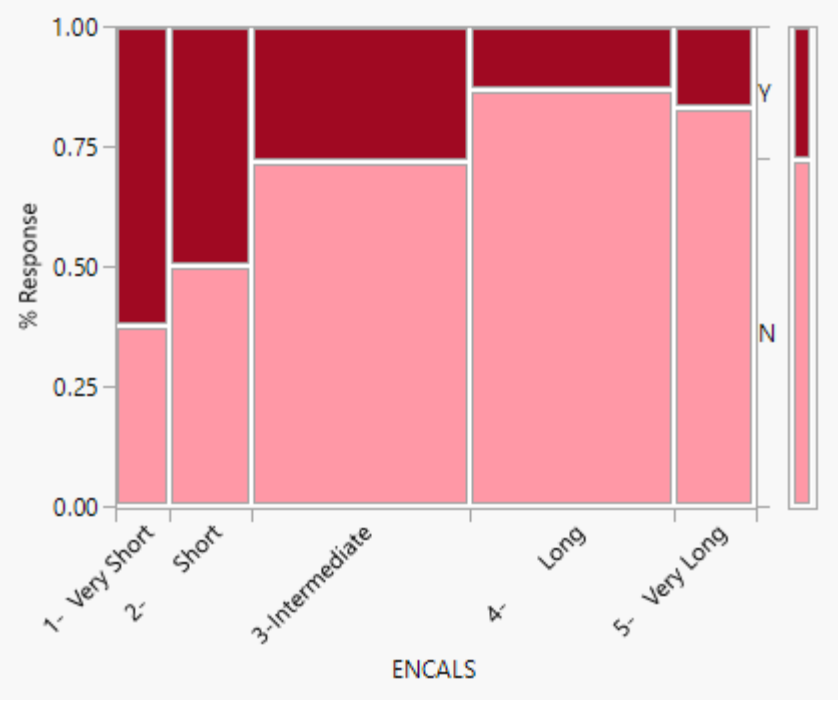
NurOwn participants



Responder

Non-Responder

Placebo participants



Responder

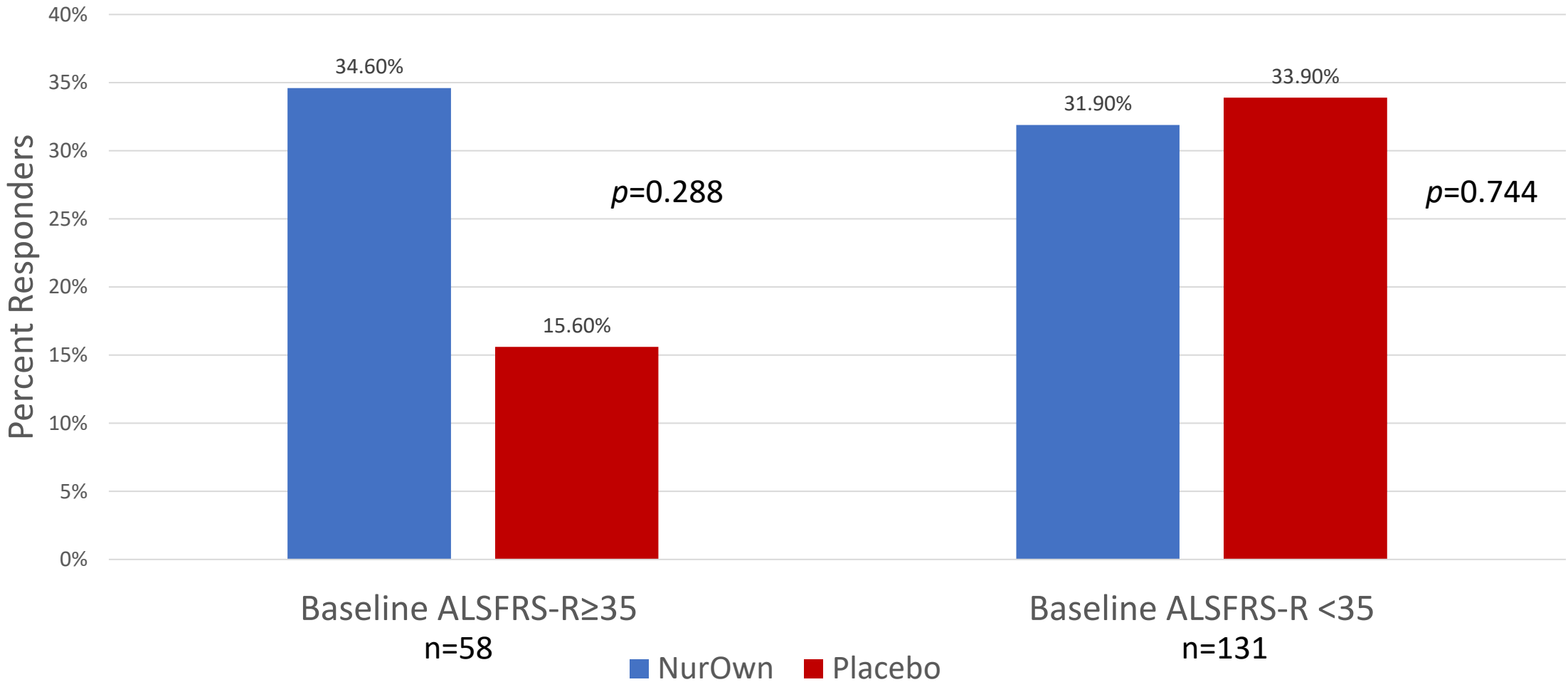
Non-Responder

Observations:

- In participants predicted to have Long to Very Long survival, there are more NurOwn responders (33%) versus Placebo (14%)
- There appears to be a paradoxical finding with a large % of responders with Placebo participants, which could point to a misclassification due to a floor effect with the ALSFRS-R, underlying biological differences or small sample size (n=8 participants in very short category)

Responder Analysis by Baseline ALSFRS-R ≥35 or < 35

Primary endpoint analyzed by baseline ALSFRS-R score, pre-specified subgroup



Post-hoc analyses using a threshold of 25 show a similar paradoxical finding in % Responders as “Very Short” ENCALS category

Conclusions

- **BCT-002, NurOwn's phase 3 trial included more participants (23%) with advanced ALS at baseline (ALSFRS-R at or below 25) compared to other trials**
- **In participants that are predicted to have long to very long survival, there are more NurOwn responders versus Placebo (33% vs 14%)**
- **The measurement of efficacy appears to be impacted in participants with more severe ALS disease at baseline by analyses focusing on both baseline ALSFRS-R and ENCALS model categories (short and very short survival)**
- **Analyses that isolate the most severely affected participants at baseline demonstrate a potential treatment effect on ALS disease progression in participants with less severe disease, an effect that is protected by randomization.**

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

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CIRM
California's Stem Cell Agency

ALS Association

I AM ALS