Further Analysis of NurOwn Phase 3 Data Based on Baseline ALSFRS-R Status Clarifies Treatment Outcomes

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brainstorm cell therapeutics

Background

Brainstorm completed a randomized Phase 3 trial in 200 ALS participants receiving 3 doses of NurOwn or placebo. The primary endpoint was a responder analysis defined as the percentage of participants with ≥1.25 points/month ALSFRS-R improvement in slope post-treatment vs pre-treatment. A key secondary endpoint was the average ALSFRS-R change from baseline to week 28. A pre-specified subgroup focused on baseline ALSFRS-R ≥35.

Inclusion criteria permitted participants with advanced ALS to be enrolled (baseline ALSFRS-R ≤ 25, 23% of study population). Participants also needed a pre-treatment decline of at least 1 point/month on ALSFRS-R. The primary endpoint was not statistically significant (Cudkowicz et al. 2022). However, the entry criteria may have obfuscated the true effect of NurOwn.

The ALSFRS-R is a bounded scale, thus at some point the slope of decline must slow, though at what level this happens is uncertain. This results in a risk that people with lower ALSFRS-R scores at baseline may experience slowing of decline due to a floor effect of the ALSFRS-R which could result in a misclassification on the primary endpoint (floor effect). Pre-specified and post-hoc subgroup analyses in evaluating the treatment effect were performed to try to minimize this effect.

A pre-specified subgroup analysis of participants with baseline ALSFRS-R ≥35 showed a trend to a meaningful increase in % responders in the NurOwn arm. This analysis included 31% of the trial participants.

Hypothesis

Participants with higher baseline ALSFRS-R are less likely to experience a floor effect on ALSFRS-R, and methods to select participants less likely to experience the ALSFRS-R floor might exclude fewer participants and yield similar results to the subgroup with baseline ALSFRS-R >35.

Methods

We performed two post-hoc sensitivity analyses focused on minimizing the ALSFRS-R floor effect by identifying and excluding participants at highest risk of being impacted by an ALSFRS-R floor effect.

- **Total Score Threshold** (TST) defined as ALSFRS-R ≤ 25
- **Item Level Threshold** (ITL) defined as participants with at 5 of 6 Fine & Gross Motor scale items with a baseline score of 0 or 1

The TST and ILT identified 23% (n=44) and 16% (n=30), of trial participants, respectively, for exclusion from the sensitivity analysis due to the impact of the ALSFRS-R floor on participant scores.

Results

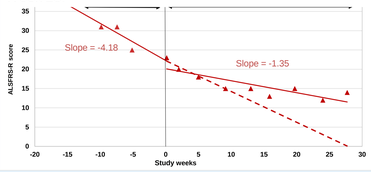
The Phase 3 mean baseline ALSFRS-R score of 30.9 (+/-6.3) included participants with rapid pre-trial progression and advanced ALS at the time of treatment[1]. Participants with advanced ALS had many ALSFRS-R items with values of 0 at baseline, after which further deterioration cannot be measured by that item. When enough items are scored 0, then the slope of decline may slow simply because ALSFRS-R is a bounded scale, which we will refer to as a "floor effect."

NurOwn Phase 3 featured participants with advanced ALS disease resulting in a floor effect[1]

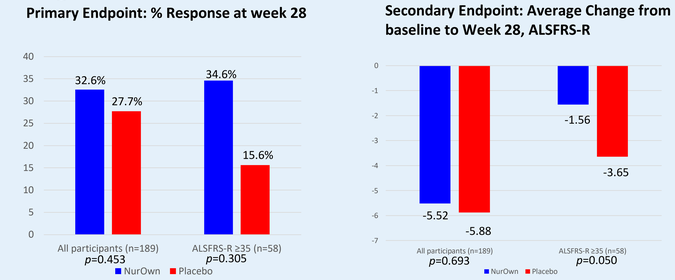
ALSFRS-R Subscale	% value of 0 at baseline	% value of 0 at Week 28[2]
Bulbar	7%	15%
Fine Motor	42%	76%
Gross Motor	37%	57%
Respiratory	1%	3%

[1] Participants with ALSFRS-R≤25: 44 of 189 (23.3%)
[2] Participants who had an ALSFRS-R at week 28 (n=31)

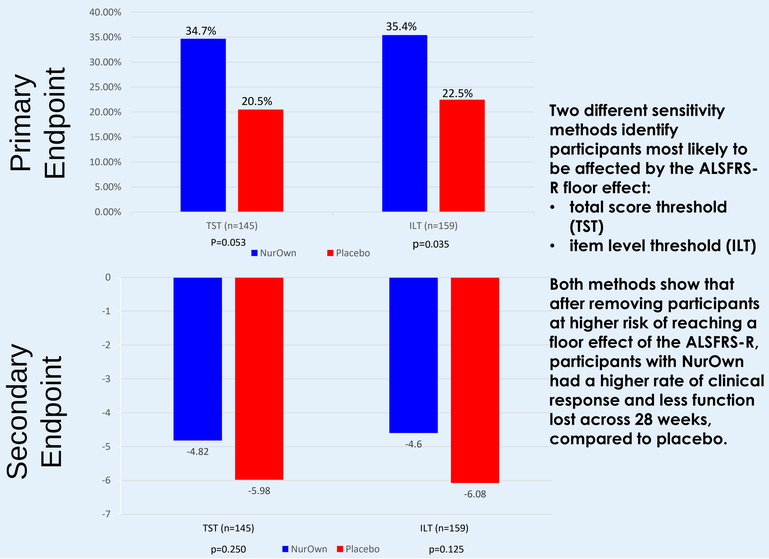
Example of clinical response and plateau of disease progression. Rate of decline in the treatment period is constrained by the remaining points on the ALSFRS-R; for the pre-treatment rate of decline to continue linearly, the participant would have had to have a score of -6 at Week 28.



NurOwn treatment suggests effect in pre-specified subgroup with less advanced disease, across endpoints



Primary Endpoint utilizing the TST and ILT to minimize the floor effect suggests treatment difference consistent with historical placebo data and power calculations

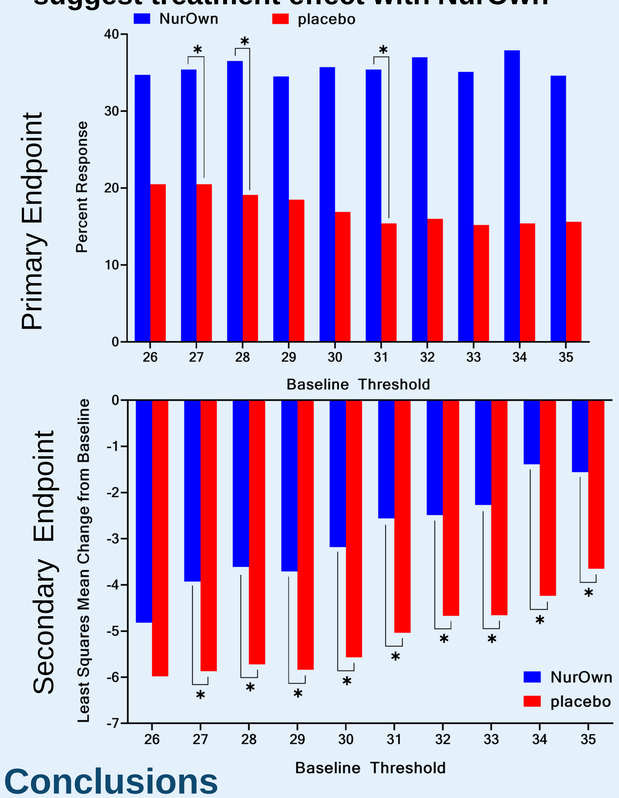


Two different sensitivity methods identify participants most likely to be affected by the ALSFRS-R floor effect:

- **total score threshold (TST)**
- **item level threshold (ILT)**

Both methods show that after removing participants at higher risk of reaching a floor effect of the ALSFRS-R, participants with NurOwn had a higher rate of clinical response and less function lost across 28 weeks, compared to placebo.

Primary and Secondary Endpoints, across baseline Thresholds minimizing the ALSFRS-R floor effect suggest treatment effect with NurOwn



NurOwn treated participants with baseline ALSFRS-R total ≥26 have 15-20% higher response compared to placebo

NurOwn treated participants with baseline ALSFRS-R total >26 have at least 2 points of function preserved compared to placebo (p≤ 0.05)

Conclusions

These sensitivity analyses demonstrate a statistical trend toward clinically meaningful treatment effects across subgroups that are consistent with the pre-specified subgroup. These sensitivity analyses are meant to minimize methodological challenges of the ALSFRS-R at the lower end of the scale.

Biomarker data recently presented at ALS One (Lindborg 2022) showed consistent patterns across biomarkers in participants with more advanced ALS at baseline that might help further delineate important subgroups and raises the possibility that all participants could be benefiting from the treatment although the ALSFRS-R floor effect makes this difficult to demonstrate in the lower part of the scale.

Careful examination of these data may have implications for evaluations of ALS therapeutics.

References

Cudkowicz, M, et al. Musc Nerve, Jan 2022, Supplemental File & Erratum Musc Nerv Aug 2022

Lindborg S. The Relationship between CSF Biomarkers and Efficacy of Treatment with NurOwn ALS One Research Symposia, Oct 2022.