Measuring the rate of impairment in ALS patients using the Revised-ALS Functional Rating Scale: Key Insights into the Floor Effect of the Scale

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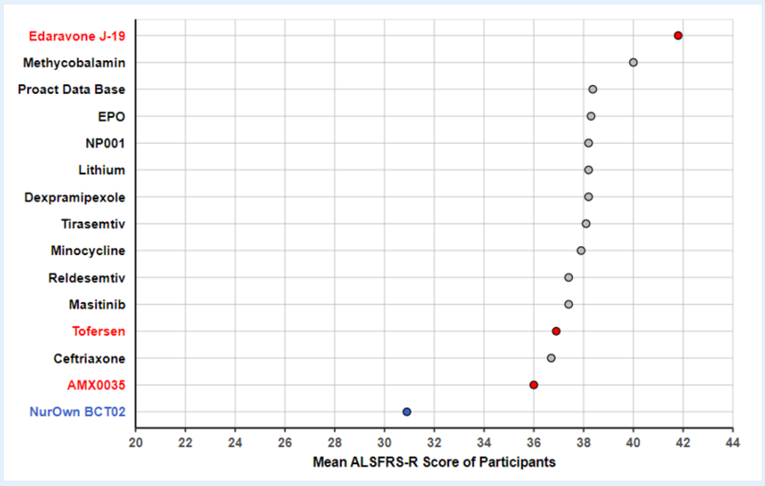
Background

Brainstorm completed a randomized Phase 3 trial in 189 ALS participants receiving 3 doses of NurOwn (MSC-NTF) or placebo (NCT03280056). 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.

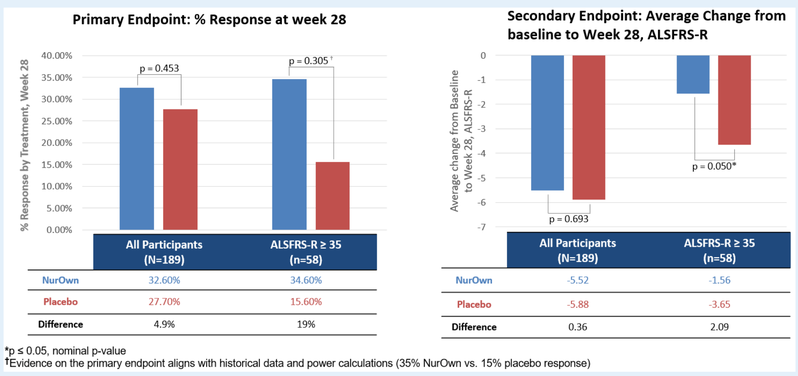
The inclusion criteria permitted enrollment of participants with advanced ALS (baseline ALSFRS-R ≤ 25, 23% of study population), resulting in a trial with much lower baseline ALSFRS-R scores as compared to other recent late-stage ALS trials. The primary endpoint was not statistically significant[1], but the pre-specified subgroup analysis of participants with baseline ALSFRS-R ≥ 35 showed a trend toward a meaningful treatment difference across endpoints. The ALSFRS-R entry criteria may have obscured the true NurOwn effect.

The ALSFRS-R is the primary tool for evaluating disability in clinical practice and in trials. While widely used, the scale is hampered by its ability to measure function in those with low functional status. The floor effect occurs when the scale of measurement is not able to capture progression at the bottom of the scale[2].

NurOwn Phase 3 trial (BCT-002) has the lowest baseline ALSFRS-R among all recent late-stage trials



NurOwn treatment suggests effect in participants with less advanced disease in pre-specified subgroup



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

	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)

Objectives

The Phase 3 NurOwn trial (BCT-002) enrolled patients with advanced ALS revealing impacts of the floor effect. To further assess this effect, BCT-002 (n=189) and PRO-ACT (n=7,712) data were evaluated to assess the presence of scale items of 0. A quantitative method[3,4] was employed to identify a functional decline pattern reflecting a floor effect with a hinge point, demonstrating a plateau in clinical data.

Methods

PRO-ACT Data: Only participants with more than 3 observations were included. If more than 1 score exists for a given day, the average was used. For algorithm stability to outliers, points with standardized residual >3 were removed. 3930 participants satisfying these conditions were analyzed.

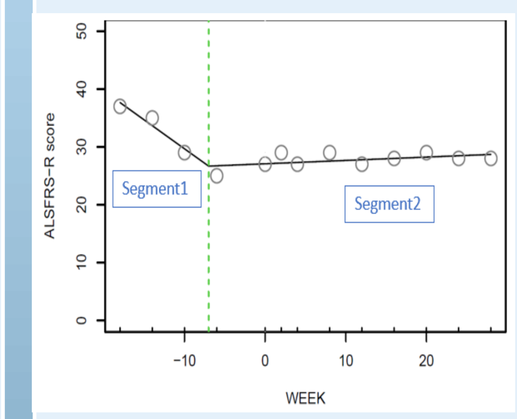
R package 'Segmented'

The package finds the hinge point via iterative fitting. It fits a piecewise linear regression or segmented regression model to the patient data; and simultaneously estimates the slopes and hinge point.

Quantitative Approach, individual participant data

1. Fit segmented regression model, estimate slope for Segment 1 and 2 (called slope1 and slope2, respectively), and the hinge point
2. Apply rules to identify participants with a floor effect pattern – a linear decline phase followed by a plateau phase.

Illustration of the method



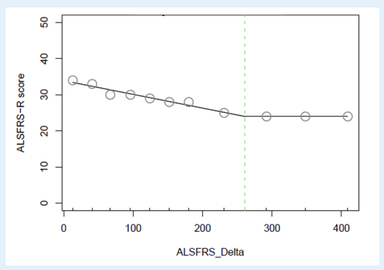
- If Slope1 < 0, participant declining in segment 1
- If Slope2-Slope1 > |Slope1|, then plateau in segment 2
- Additional checks:
  1. segment 1 truly decline phase
  2. segment 2 truly plateau phase

Results

- 185 of 3930 (4.7%) PRO-ACT participants exhibited a floor effect pattern with the average (SD) hinge point occurring at an ALSFRS-R score of 25 (11).
- 21 of 94 (22.3%) NurOwn Phase 3 trial placebo participants exhibited a floor effect pattern with the average (SD) hinge point occurring at an ALSFRS-R score of 27 (9).
- Visual inspection of each participant identified as having a hinge point and the small variability in segment 2 suggest data after the hinge point in these participants reflected a plateau.

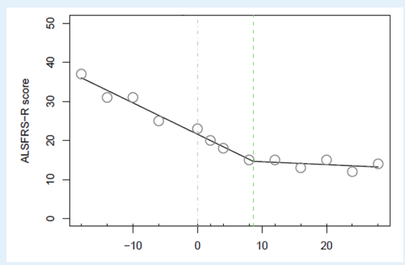
PRO-ACT example

All 6 Fine and Gross Motor items reached 0 during the trial



BCT-002 Placebo example

5 of the 6 Fine and Gross Motor items reached 0; and 2 of 3 Respiratory items reached 0 during the trial

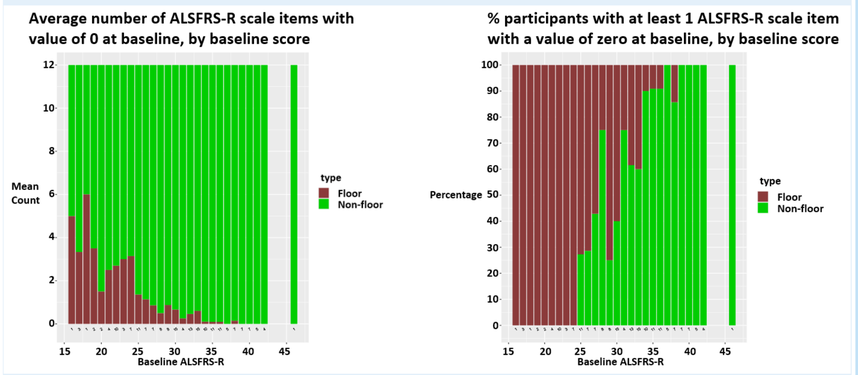


Plateau Participants show elevated rate of 0's across FM and GM items illustrating plateau was driven by ALSFRS-R floor effect

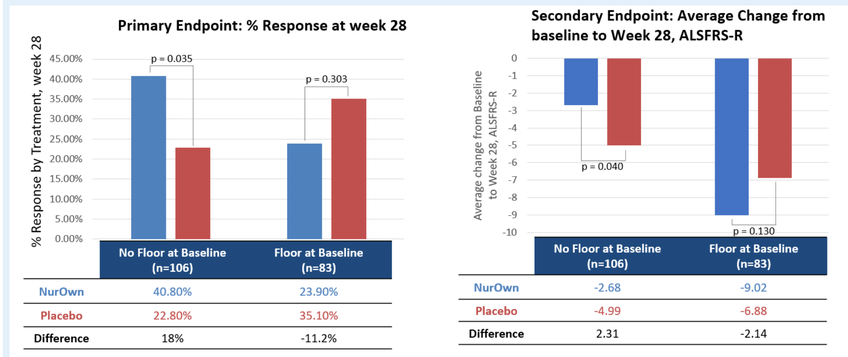
% patients with item = 0 anytime during the trial	BCT-002 (N=21)			PRO-ACT (N=140)*		
	Item 1	Item 2	Item 3	Item 1	Item 2	Item 3
Bulbar	14%	14%	10%	8%	6%	8%
Fine Motor	43%	48%	38%	25%	30%	30%
Gross Motor	33%	29%	62%	15%	10%	44%
Respiratory	5%	5%	0%	4%	6%	1%

* only those with itemized score at baseline are included

BCT-002 Participants with Lower Baseline ALSFRS-R Scores Had Greater Impact of item level Floor Effect; Impact of Floor Effect Decreased with Higher Baseline Scores



BCT-002 Participants Receiving NurOwn with No Evidence of Floor Effect at Baseline Suggests Treatment Effect



	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%

	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

No floor at Baseline defined as participants with all baseline ALSFRS-R items ≥ 1 (green above)
Nominal p-values reported

Conclusions

- A plateau in ALSFRS-R scores and scale items of 0 was observed in BCT-002 and PRO-ACT, suggesting measurement challenges in those with advanced ALS due to the floor effect of ALSFRS-R.
- Analyses conducted on those not impacted by the floor at baseline in BCT-002 revealed statistically significant, clinically meaningful treatment effects with NurOwn on the primary and key secondary endpoints.
- For future trials, these data suggest that analyses of participants with ALSFRS-R item score ≥2 be pre-specified.

References

1. Cudkowicz, M, et al. Musc Nerve, Jan 2022, Supplemental File & Erratum Musc Nerv Aug 2022
2. 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)
3. Muggeo, V.M.R. (2003) Estimating regression models with unknown break-points. Statistics in Medicine 22, 3055–3071.
4. Muggeo, V.M.R. (2008) Segmented: an R package to fit regression models with broken-line relationships. R News 8/1, 20–25.