ALS Phase 3 NurOwn Trial: Insight into the primary outcome through ENCALS modeled trajectories

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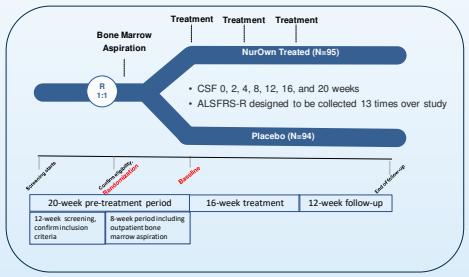
brainstorm cell therapeutics

Background

The NurOwn (MSC-NTF cells) phase 3 trial included a number of participants with advanced ALS disease (ALSFRS-R<25), making this trial subject to the impact of floor effects and reduced ALSFRS-R sensitivity (Hartmaier 2022, Mandrioli 2015). These participants had individual ALSFRS-R items of 0 at baseline, impacting treatment estimates as further functional loss cannot be measured even as a patient's condition deteriorates (Cudkowicz 2022).

Study Design and Methods: BCT-002-US

- Randomized, double-blind, placebo-controlled Phase 3 study
- 189 ALS participants enrolled with ALSFRS-R ≥25 at screening and ≥3 ALSFRS-R point decline in 12 weeks pre-randomization
- Primary Endpoint, Clinical Response: participants with a ≥1.25 points/month improvement between pre- and post-treatment slope



- The ENCALS model (Westeneng 2018) is a composite endpoint developed and validated on European data to reliably estimate prognosis trajectories using a set of predictors
  - identifies participants most likely to reach the composite survival endpoint in a "very-short" and "short" period
  - we used the model to understand our data, due to the rich set of covariates that it employs to predict progression, and to identify those most likely impacted by the ALSFRS-R floor effect
  - BCT-002 allows the opportunity to apply the model to US data
- Clinical efficacy was evaluated using the Primary Endpoint comparing methods (ENCALS and ALSFRS-R baseline) designed to minimize misclassification of clinical response in BCT-002-US

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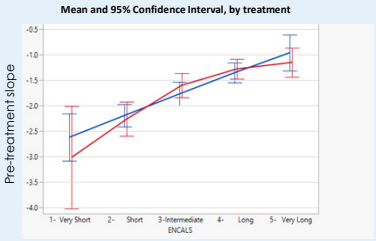
Results

ALSFRS-R floor effect evident in BCT-002-US: Participants with advanced ALS disease had a high rate of ALSFRS-R items with values of 0 at baseline

ALSFRS-R ≤ 25 at baseline	Item 1	Item 2	Item 3	Average
Bulbar subscale, %	11%	7%	2%	7%
Fine Motor subscale, %	43%	43%	39%	42%
Gross Motor subscale, %	23%	14%	75%	37%
Respiratory subscale, %	0%	2%	0%	1%

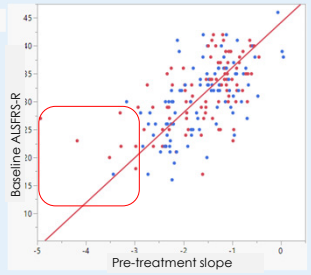
BCT-002-US baseline relationships



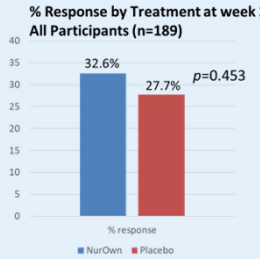
Participants predicted to live shorter have higher pre-treatment slopes

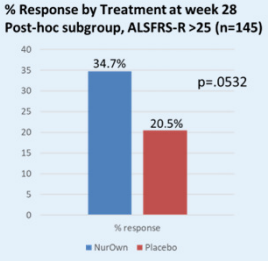
There are participants with large rates of decline pre-treatment, which are predominantly in the Placebo Group, and are misclassified as a responders when they represent a floor effect

These are visible in both ENCALS "very short" and Baseline ALSFRS-R value

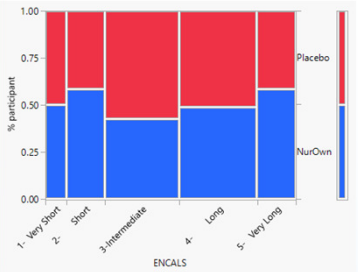


Treatment effect not statistically different in overall study, Suggests effect in mild/moderate ALS



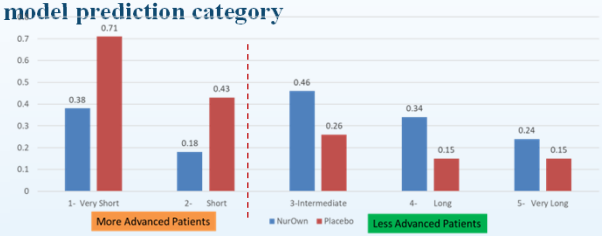


ENCALS: BCT-002-US enrolled a broad set of participants



BCT-002 ENCALS model prediction	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

Primary Responder Endpoint presented by ENCALS model prediction category



- Participants with ENCALS model prediction of Intermediate to Very Long survival suggests NurOwn treatment effect 36% NurOwn response versus 21% Placebo (p=0.056) and are aligned with statistical assumptions based on PRO-ACT data.
- In the more advanced participants predicted to have "very short" and "short" survival, there was a paradoxical finding with an increased rate of response with Placebo (52%), which may suggest a misclassification error of treatment response related to an ALSFRS-R floor effect. This finding appears to be driven by a few outliers (e.g., > 3 points/month decline).

Conclusions

- BCT-002-US, NurOwn's phase 3 trial included a high number of participants with advanced and rapidly declining ALS.
- We saw a treatment effect in participants predicted by the ENCALS model in Intermediate to Very Long survival
  - These categories are less likely to be influenced by scale challenges
- Participants with high rate of decline by ALSFRS-R and predicted Very Short and Short survival with ENCALS may have been misclassified due to ALSFRS-R floor effect, which favored the placebo group.
- ALS trials should be careful of the ALSFRS-R floor effect when including participants that are rapidly progressing (Very Short and Short ENCALS model), including when having a delayed period between screening and baseline.