ALS Case Study: Clinical Trial Designs for Small Patient Populations

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Everylife Foundation Scientific Workshop
CONCEPTUALIZING AN FDA RARE DISEASE CENTER OF EXCELLENCE
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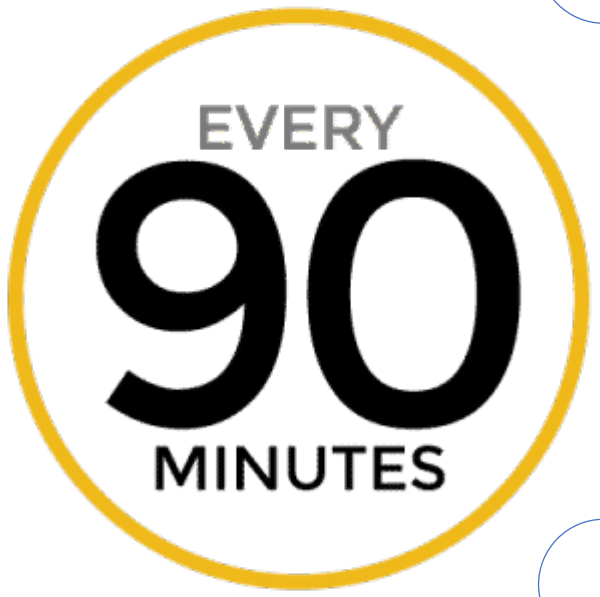
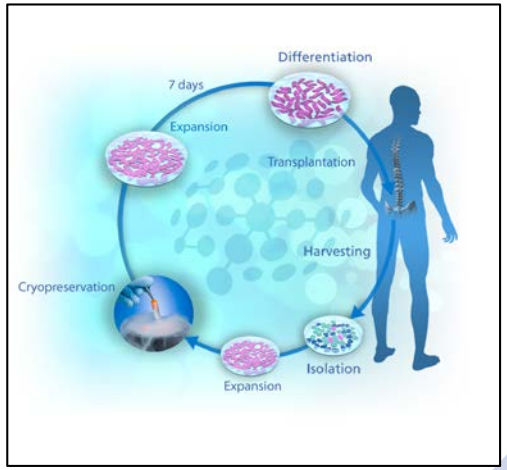


- Affects ~30,000 people in US
- ~6000 new cases per year in US
- $250,000 per year cost of care
- Diagnostic delays are common
- 51 clinical trials, 2 approved therapies

Clin Neurol Neurosurg 2012, J Neurol Sci 2014

Development



2007
NurOwn Technology Developed

2010-2014 Phase 1/2a Open Label Studies 26 participants

2014-2016 Phase 2 randomized study 48 participants

2017 + Phase 3 randomized study 200 pa

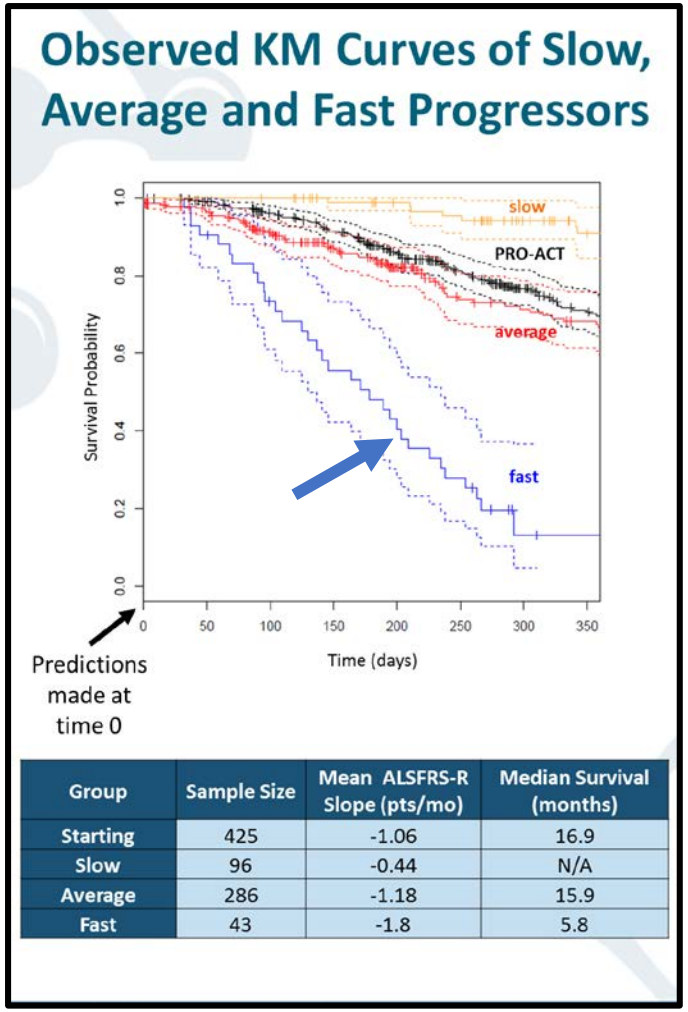
ALS clinical trial design

brainstorm cell therapeutics

- Rapid progressors and shorter time to diagnosis → predictable decline (prognostic enrichment) ✓
- Rapid progressors → more likely to respond to ALS therapy (predictive enrichment) ✓
- Use of rapid progressors→ increases ALS study power (reduced study sample size) ✓
- Pre-post ALS treatment design → ALSFRS-R slope change (responder analysis) ✓

Prognostic Enrichment

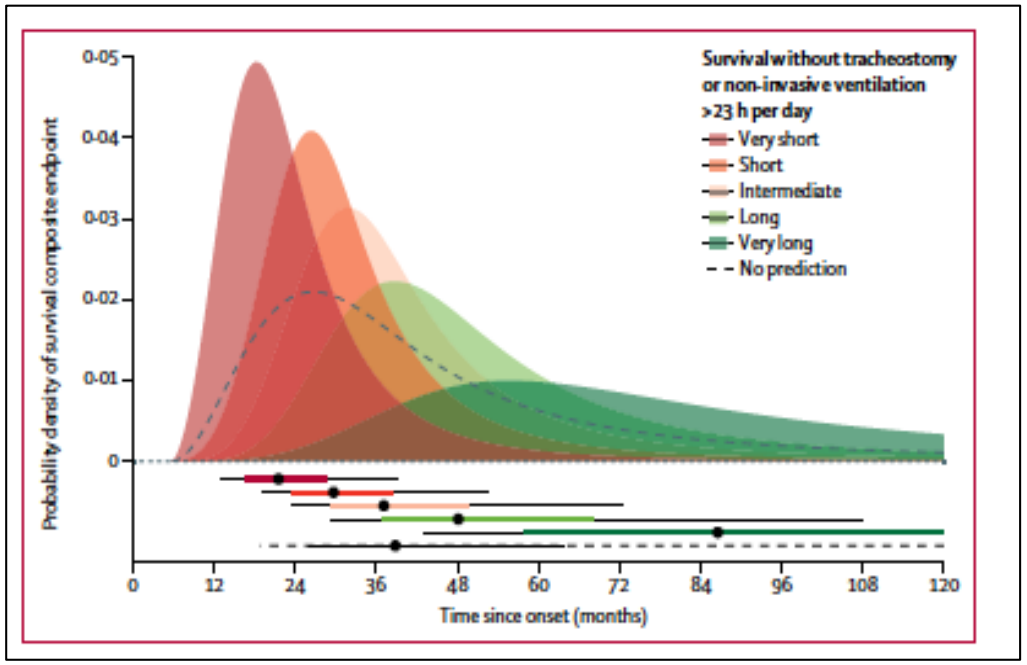
rapid progressors: strong correlation with survival

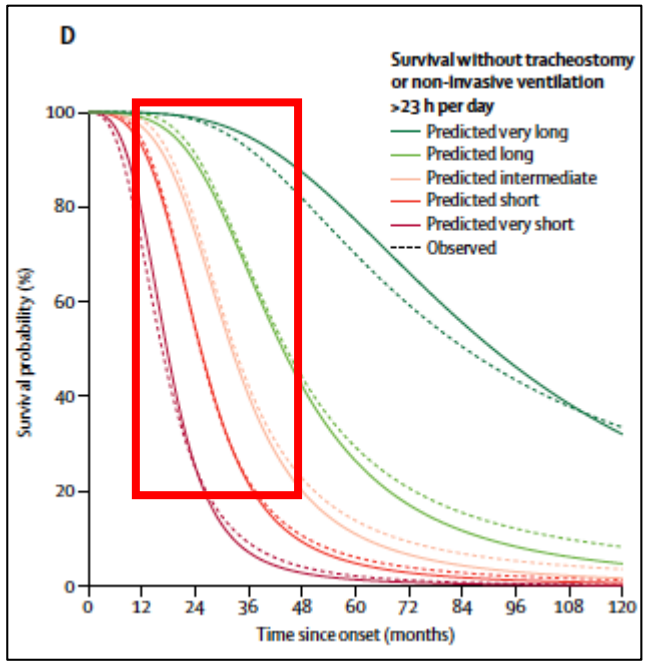


Group	Sample Size	Mean ALSFRS-R Slope (pts/mo)	Median Survival (months)
Starting	425	-1.06	16.9
Slow	96	-0.44	N/A
Average	286	-1.18	15.9
Fast	43	-1.8	5.8

Machine learning Models for the Clinical development of Gene and cell Therapies
Albert Taylor et al, Origent Data Sciences, Poster presentation

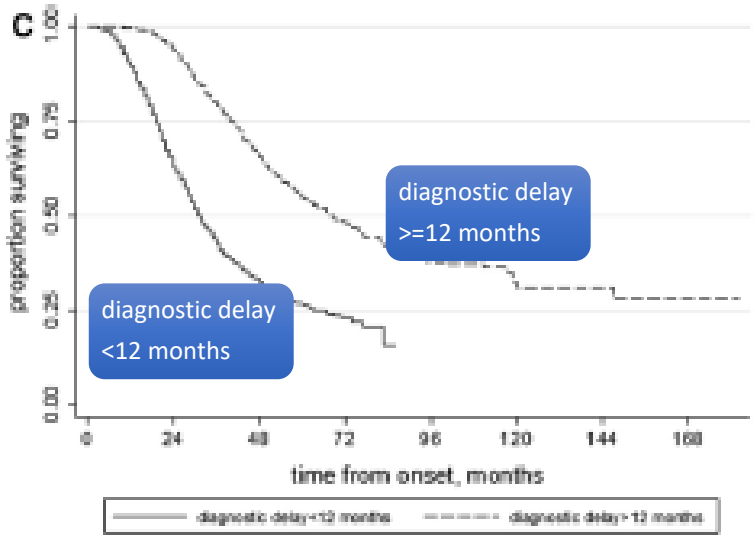
Prognostic Enrichment: ALS rapid progressors show less clinical variability and more predictable rates of decline





Adapted from Westeneng, Lancet Neurology 2018.

Prognostic Enrichment: Shorter time to ALS diagnosis identifies group with more rapid decline



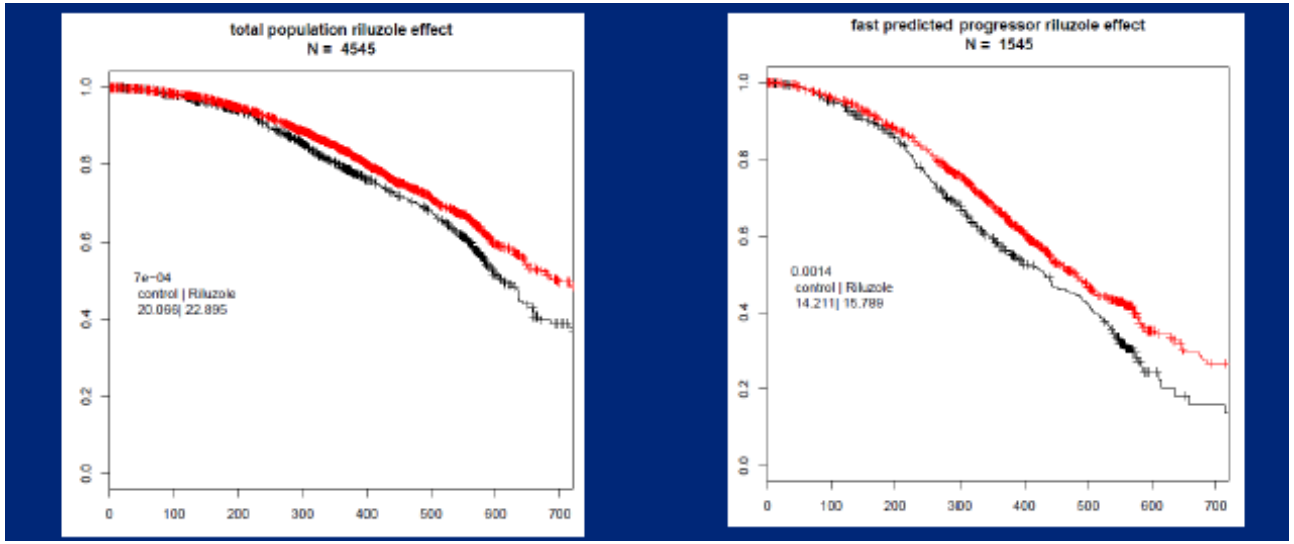
J Neurol 2017

Predictive Enrichment:

Rapid Progressor Subgroup Showed Greater Response to Riluzole

Total Population

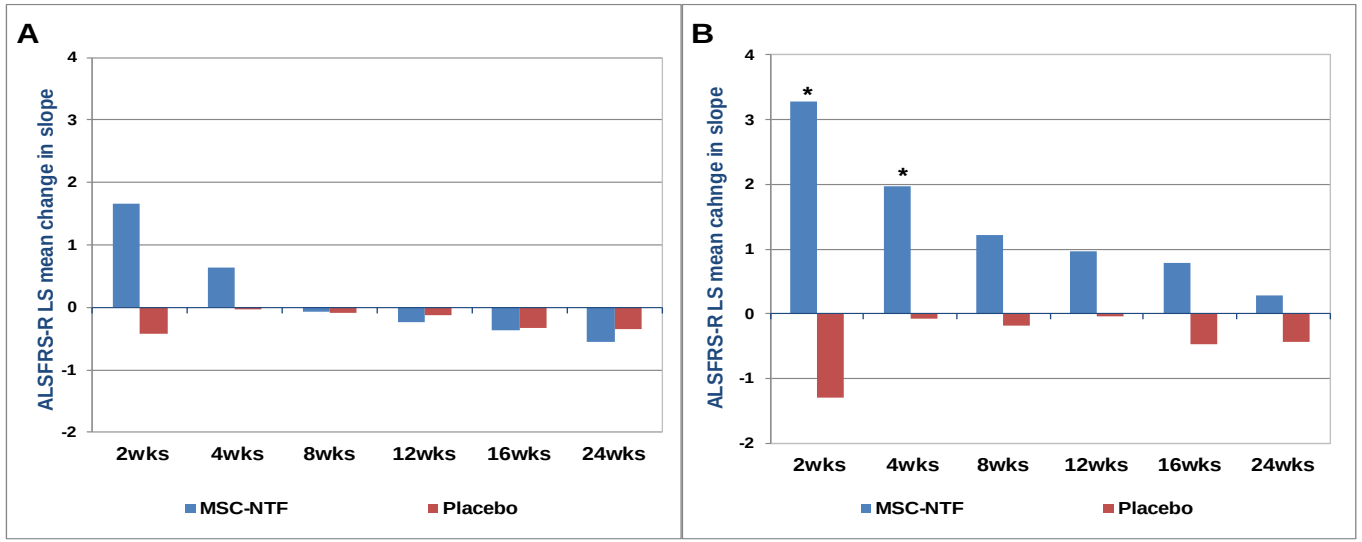
Rapid Progressor Subgroup



Fournier CN, et al. Enriched clinical trial cohorts improve study power. 16th Annual NEALS Meeting, Tampa, FL, USA, October 4, 2017

Predictive Enrichment:
Rapid Progressor Subgroup Showed Greater Response to NurOwn®

All participants (n=46)	Rapid progressors (n=21)

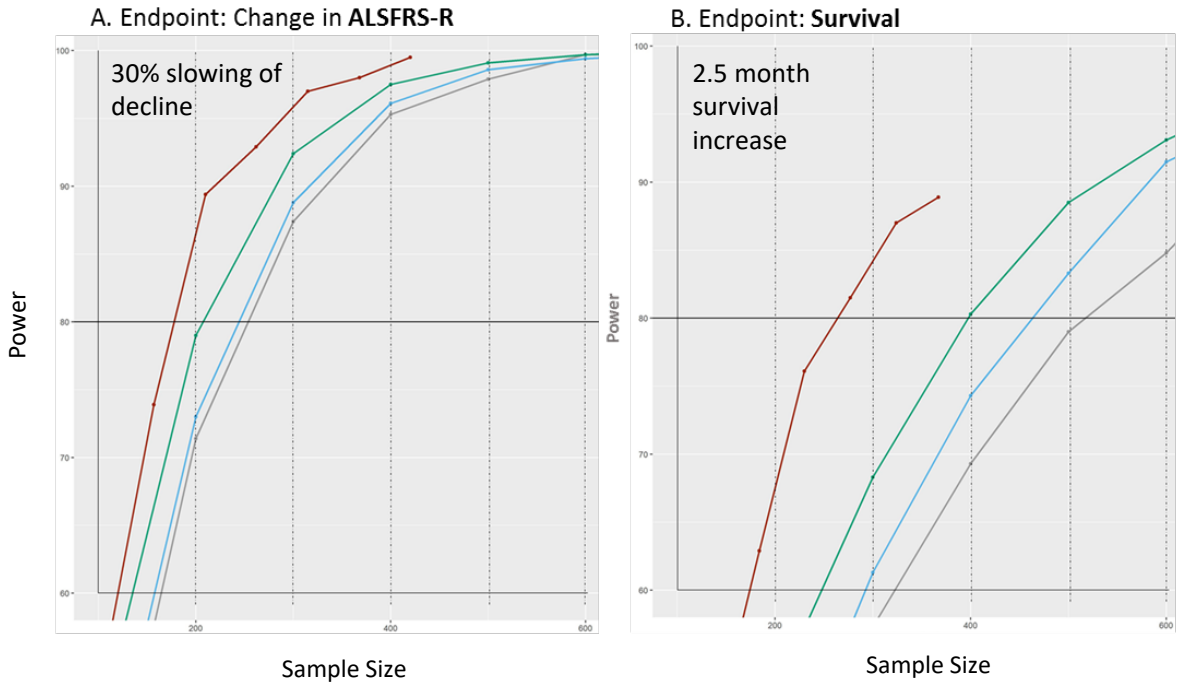


NurOwn Phase 2 RCT

* p<0.05 (two-sided T test)

Study Power:

enrichment can reduce ALS



ORIGINAL CONTRIBUTION

Can Selection of Rapidly Progressing Patients Shorten Clinical Trials in Amyotrophic Lateral Sclerosis?

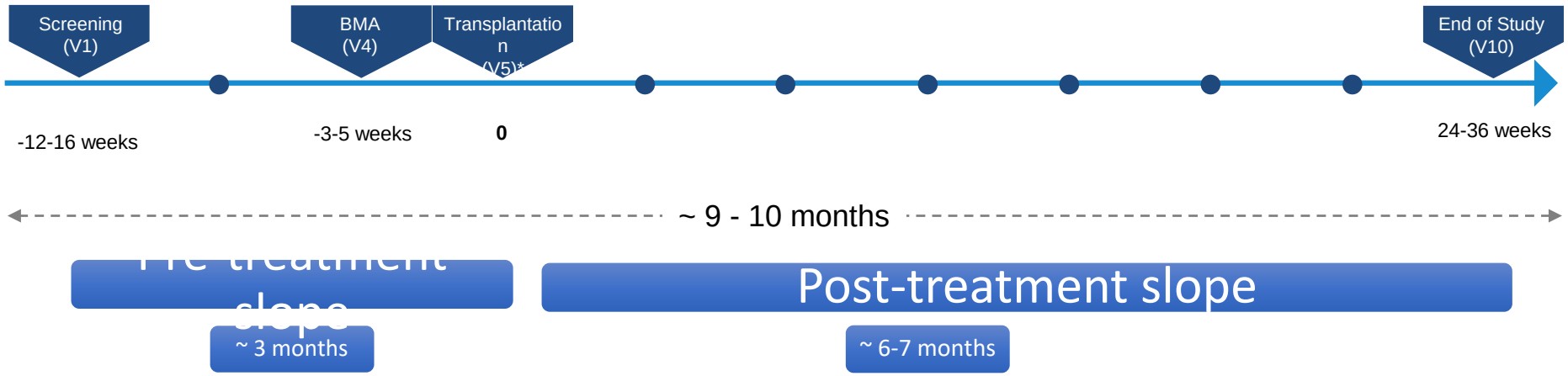
Mamede de Carvalho, MD; Michael Swash, MD

***Archives of Neurology* 2006**

Key	Randomization Strata	Enrollment/ Analysis Strata
	Random #	None
	Traditional	None
	Algorithmic	None
	Algorithmic	Predicted strata

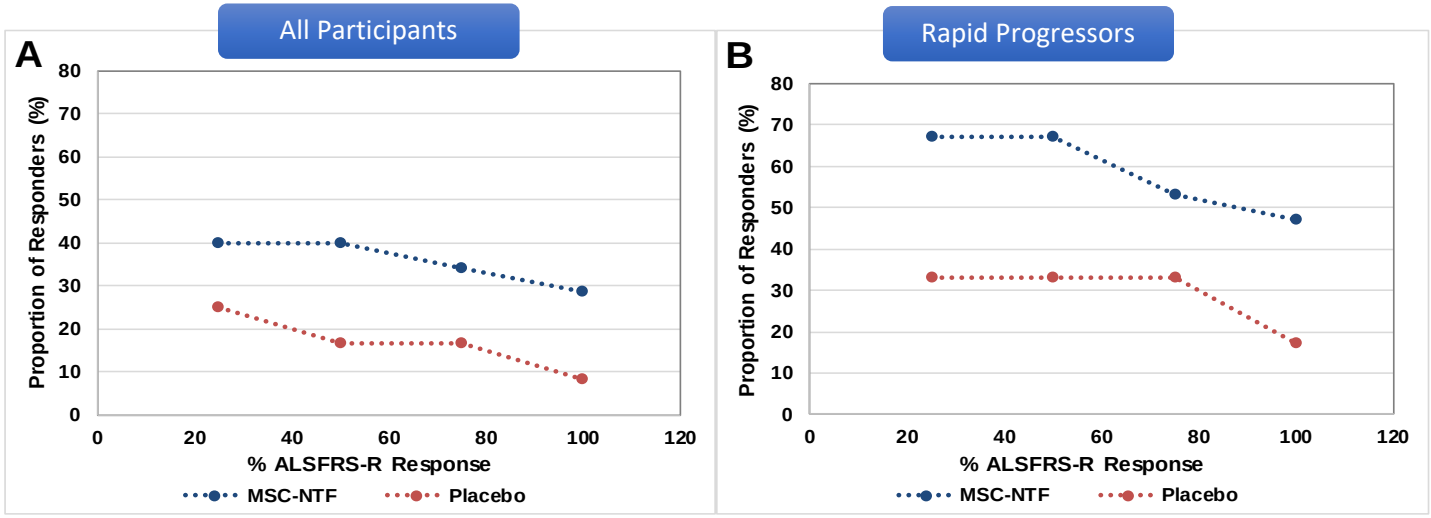
ORIGENT DATA SCIENCES

Responder Analysis*: Pre-post treatment ALSFRS-R slope reduces heterogeneity and identifies responders

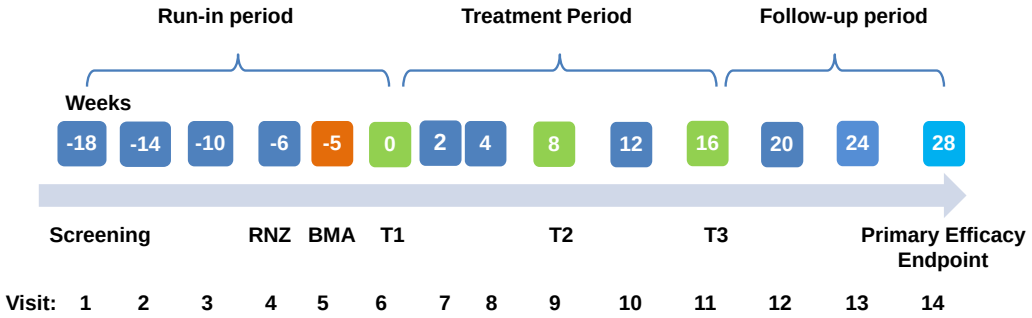


*Phase 2 NurOwn® Study Design

Responder Analysis: Cumulative Probability of Responder Analysis (CPRA) 12 weeks post transplantation



BCT-002-US Phase 3 Study Design



-5 **BMA: Bone Marrow Aspiration**
RNZ: Randomization
0 ***T1, T2, T3:*** **Treatments 1, 2 and 3, respectively**

ALSFRS-R: will be assessed at all time points except at BMA visit
Blood and CSF will be collected for biomarker analyses at visits 6 through 13

Disease duration < 2 years (inclusion criteria)

Rapid progressor subgroup (inclusion criteria)

Pre-post treatment slope responder analysis (study design)

Thank you