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

NurOwn®

Development

“No time to waste”

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 participants
ALS clinical trial design

- 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

Observed KM Curves of Slow, Average and Fast Progressors

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

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

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)

A

B

* p<0.05 (two-sided T test)
Study Power: enrichment can reduce ALS
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.

A) All Participants

B) Rapid Progressors
BCT-002-US Phase 3 Study Design

- **Run-in period**
  - Weeks: -18, -14, -10, -6, -5, 0, 2, 4, 8, 12, 16, 20, 24, 28
  - Visits: 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14

- **Treatment Period**
  - Visits: 12, 16, 20, 24, 28

- **Follow-up period**
  - Visits: 12, 13, 14

**Inclusion Criteria**
- Disease duration < 2 years
- Rapid progressor subgroup

**Endpoints**
- Primary Efficacy Endpoint
- Pre-post treatment slope responder analysis

**Additional Notes**
- BMA: Bone Marrow Aspiration
- RNZ: Randomization
- 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
Thank you