Use of a Prediction Algorithm for Stratification in an Amyotrophic Lateral Sclerosis Study
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Introduction
Amyotrophic lateral sclerosis (ALS)
ALS is a neurodegenerative disorder that affects motor neurons in the central nervous system.
Clinical manifestations of the disease may include limb atrophy, impaired speech and swallowing, and death.

An algorithm for predicting ALS progression
The clinical phenotypes and rates of disease progression of ALS are highly variable.
This heterogeneity presents challenges for clinical trial design.
Lead-in periods have been used to predict ALS disease progression in clinical trials, but lead-in periods have limitations.
Disease progression slopes derived from lead-in periods are not always predictive, as ALS-related decline in function may not be linear.
Lead-in periods lengthen the duration of clinical trials and extend the time from enrollment to administration of study drug.

To advance the ability of researchers and clinicians to predict ALS disease progression, an algorithm was developed to predict disease progression in ALS on the basis of information in patients' records (Figure 1).
This algorithm is one of the 2 award-winning algorithms from the DREAM Phil Bowen ALS ProSafe Challenge, in which a limited dataset from the Pooled Resource Open-Access ALS Clinical Trials (PRO-ACT) was provided to developers.
The algorithm performed well in a larger portion of the dataset versus clinician predictions.
This algorithm predicting ALS progression was used in an exploratory post hoc analysis of an open-label RCI study.
In the ongoing randomized controlled RCI trial (NCT03068754), the algorithm replaced the lead-in phase for stratifying patient randomization (Part 2).

Methods
Part 1: Assessment of a revised prediction algorithm for ALS progression in an open-label RCI pilot study
Pilot study design
Forty-three patients with ALS were randomly assigned to 1 of 4 RCI dosing regimens in an 8-week open-label period followed by an optional 26-week open-label extension and taper (Figure 2).

Part 2: Ongoing randomized controlled RCI study
As of January 19, 2018, 23 subjects have been randomized (Table 2).

Results
Part 1: Open-label RCI pilot study
A modified prediction algorithm for ALS progression was cross-validated using a subset of PRO-ACT data and showed better performance than the original algorithm (root mean square error, 0.571 and 0.670, respectively).
The actual decline in ALSFRS score during the 9 months of the pilot study was numerically slower than, but not significantly different from, the predicted rate (Table 1).

Table 1. Comparison of the observed decline in ALSFRS score during the pilot study versus that predicted by the algorithm

<table>
<thead>
<tr>
<th>Statistic</th>
<th>Actual Slope from Pilot Study</th>
<th>Predicted Slope from Algorithm</th>
<th>P value*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean [SD]</td>
<td>−0.51 ± 0.57</td>
<td>−0.75 ± 0.26</td>
<td>0.087</td>
</tr>
<tr>
<td>Median [IQR]</td>
<td>−0.36 [-1.21, 0.36]</td>
<td>−0.79 [-1.20, -0.29]</td>
<td></td>
</tr>
</tbody>
</table>

Part 2: Ongoing randomized controlled RCI study
As of January 19, 2018, 23 subjects have been randomized (Table 2).

Table 2. Enrollment in the ongoing, randomized, multicenter, double-blind, placebo-controlled study as of January 19, 2018

<table>
<thead>
<tr>
<th>Enrollment Category</th>
<th>No. Sites activated</th>
<th>No. of Sites (all United States)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total</td>
<td>26</td>
<td>(all United States)</td>
</tr>
<tr>
<td>Sites activated</td>
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<td></td>
</tr>
<tr>
<td>Patients screened</td>
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<td></td>
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<tr>
<td>Patients in screening</td>
<td>6</td>
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<tr>
<td>Patients randomized</td>
<td>23</td>
<td></td>
</tr>
<tr>
<td>Patients discontinued</td>
<td>3</td>
<td></td>
</tr>
</tbody>
</table>

Conclusions
Part 1: Open-label RCI pilot study
A revised prediction algorithm for ALS progression was cross-validated and shown to be more accurate than the original algorithm.

Part 2: Ongoing randomized controlled RCI study
This study will be the first to incorporate a prediction algorithm for rate of disease progression rather than using a lead-in phase to stratify random assignment of patients with ALS.

References