Interaction (nonuniformity) of ALS progression and the efficacy of MN-166 (ibudilast)

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Introduction

Given the highly variable rate and form of disease progression among ALS patients (Watanabe et al 2016), the large dispersion of ALSFRS-R scores reported in clinical studies may contribute to the failure to achieve statistical significance in disease progression evaluation.

MN-166 (ibudilast), a small molecule that inhibits selective phosphodiesterase subtypes (PDEs) and macrophage migration inhibitory factor (MIF), is in clinical development for the treatment of ALS.

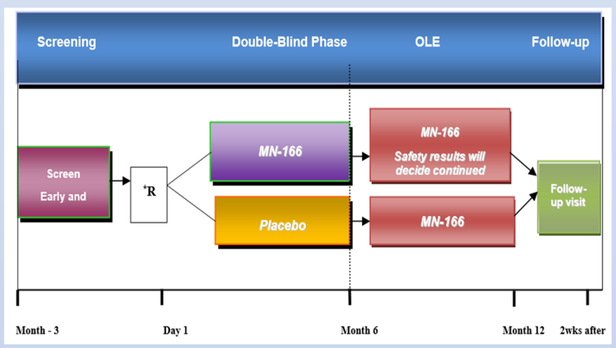
Objective

We performed Stepwise regression analysis to identify the factors that have an impact on the treatment effect of MN-166 as assessed by the ALS score.
We hypothesized that ALS disease history (time from first ALS symptom onset to trial enrollment) might have substantial effect on responsiveness to drugs.

Background

In the single-center, double-blind, placebo-controlled, clinical trial evaluating MN-166 in ALS patients (MN-166-ALS-1201), a total of 51 subjects (34 in the active group, 17 in the placebo group) without NIV support were enrolled. There was a greater number of treatment responders (stabilized or improved ALSFRS-R score from baseline to end of 6 months treatment) in the MN-166 group than in the placebo group although this finding did not reach statistical significance.
These results led us to investigate which background factors of patients' characteristics reasonably predict both ALS disease progression and treatment efficacy.

MN-166-ALS-1201 trial Design



Major Inclusion Criteria
- Age 18-80 yrs,
- Dx of Familial or sporadic ALS
- ALS with onset of ≤ 5yrs
- SVC ≥ 60%
- On stable dose of Riluzole

Major Exclusion Criteria
- On NIV, tracheostomy

2 treatment arms: MN-166 and matching placebo;
Randomization occurred in a 2:1 ratio (MN-166: placebo).
MN-166 (30 mg BID) or matching placebo were administered as an adjunct to riluzole (50 mg BID)
Subjects received MN-166 for an additional 6 months in the open-label phase

Baseline Characteristics

Baseline Characteristics	Placebo (N=17)	MN-166 (N=34)
Age	57.5 years	59.2 years
Gender Male Female	 12 (70.6%) 5 (29.4%)	 23 (67.6%) 11 (32.4%)
Family History of ALS (Yes)	2 (11.8%)	2 (5.9%)
Months from first onset	28.8 months	17.9 months
Site of disease onset (Limb)	16 (94.1 %)	25 (73.5%)
Baseline ALSFRS-R score	39.0	39.3

Overall, baseline characteristics between the MN-166 vs. placebo groups were generally similar.

However, mean months since first symptom onset was shorter for the MN-166 vs placebo treatment groups, 17.9 vs 28.8 months.

Methods

Regression Tree Analysis and Multiple Regression Analysis were used to evaluate the potential factors that affect treatment effects. Evaluated factors were gender, age, race, site of onset (upper limb, lower limb, bulbar onset) UMN/LMN symptom involvement, and ALS history at trial enrollment (latency between trial enrollment and first ALS symptom).

Correlational Analysis was conducted to analyze the correlation between
(1) ALS history and baseline ALSFRS-R score
(2) ALS history and disease progression, measured as change in ALSFRS-R score from baseline to end of 6 month treatment

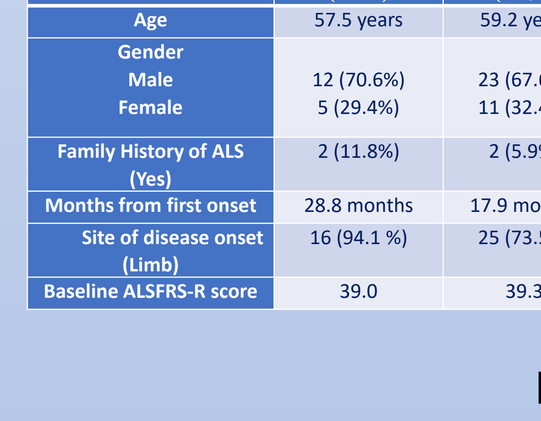
Results

Regression Tree Analysis

Regression Tree Analysis analyzes the impact on treatment effect by the combination of factors.

It was suggested that site of onset (bulbar onset Yes or No) and ALS history (cut off days is 618 days on symptom) are the substantial factors that have an impact on treatment effect.

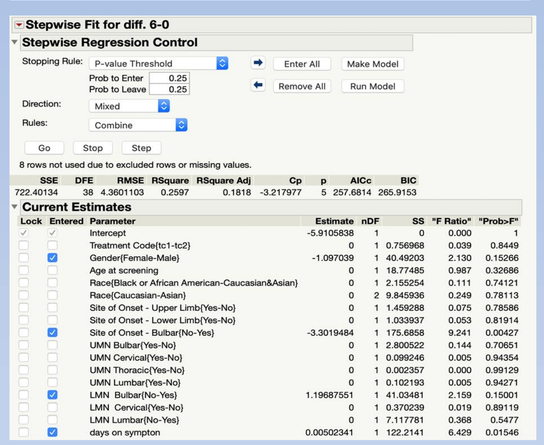
Red dot=placebo group **Blue dot** =MN-166 group



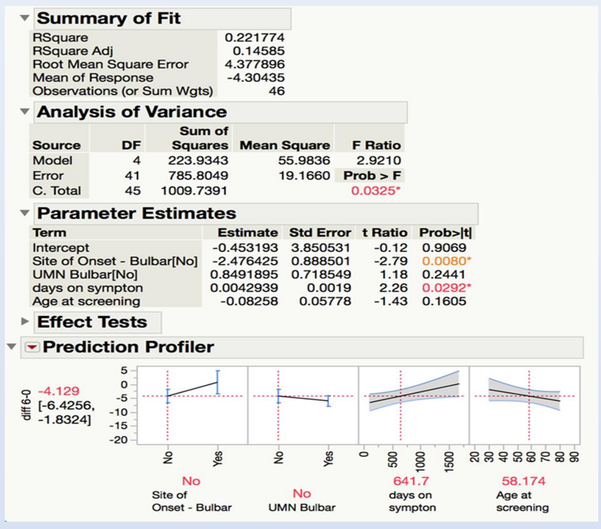
Multiple Regression Analysis (Stepwise Regression)

Multiple Regression Analysis analyzes the impact on the overall drug effect of each factor.

Stepwise Regression further narrowed down that gender, bulbar onset, LMN bulbar symptom and ALS history (i.e. days since first onset of symptom) are the factors affecting treatment effect.



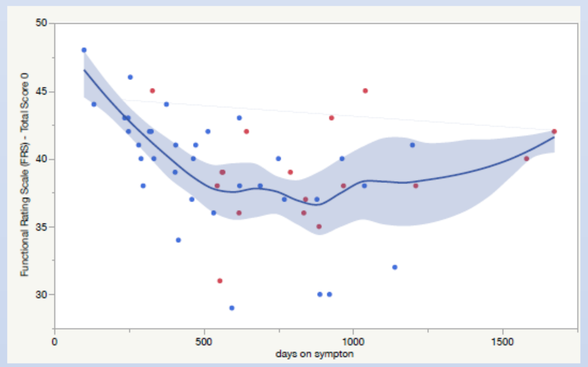
Result (continued)



"Bulbar onset" and "ALS history" (i.e. days from first onset of symptom) were identified as the factors that were statistically significant (p< 0.05).

Bulbar onset was considered as a "statistically important factor" and "ALSFRS-R score progression" was milder in the Bulbar onset group as determined by regression tree analysis.

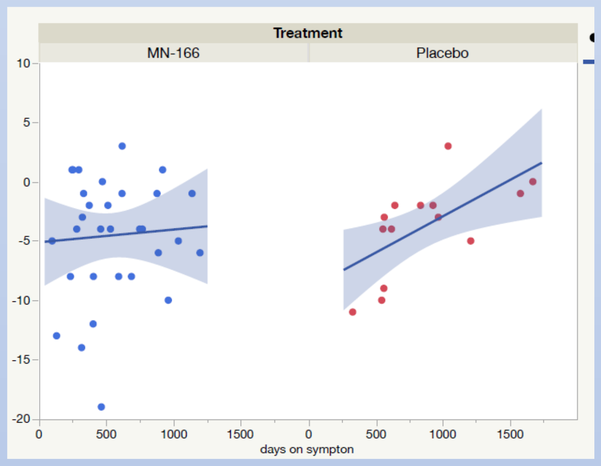
However, since there are only 9 patients in Bulbar onset group, a fair comparison between the active and placebo groups was difficult. We then focused on the ALS history, another important factor that potentially affects treatment effect.



ALS History & Baseline ALSFRS-R score Functionality

A significant negative correlation (-0.72, p<0.01) was observed between ALS history and baseline ALSFRS-R scores in patients with ALS onset <600 days prior to enrollment (i.e. short ALS history). Patients with ALS onset >600 days prior to enrollment (i.e. long ALS history) had greater variability in baseline ALSFRS-R scores.

x axis: ALS history (Days from first onset of symptom to trial enrollment)
y axis: ALSFRS-R total score at Baseline
Red dot=placebo group Blue dot =MN-166 group

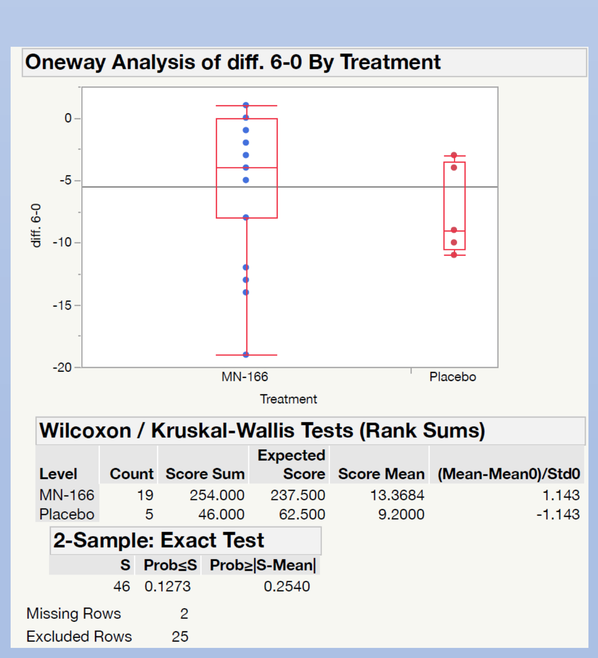


ALS History, Disease Progression & MN-166 Efficacy

A significant positive correlation (0.63, p<0.05) was observed between ALS history and ALS disease progression in the placebo group. Without MN-166 treatment, greater disease progression was observed in short ALS history patients (*Figure 2 Right*).

On the other hand, no correlation (point estimate=0.06, p=0.73) was observed between ALS history and ALS disease progression in the MN-166 group (*Figure 2 Left*).

x axis: ALS history at enrollment
y axis: ALSFRS-R progression from baseline to Month 6
Red dot=placebo group Blue dot =MN-166 group



Wilcoxon Rank-sum Test

The p-value was 0.254 with Exact test when limited to patients with ALS history ≤ 570 days.

Although it was not statistically significant, the p-value improved when focused on the subgroup with short ALS history. Taken together with the analysis results reported herein, patients with short ALS history might benefit more from MN-166 treatment than those with long ALS history.

Conclusions

- A significant negative correlation between higher baseline ALSFRS-R scores at enrollment and ALS history (time from first symptom to trial enrollment) was observed in short ALS history patients, but not in long ALS history patients.
- A significant correlation between ALS progression and ALS history was observed in the placebo group. However, it was found that this correlation was lost in the MN-166 group and was attributed to treatment effect in several short ALS history patients
- Despite the study's randomization design, there were meaningful differences found in ALS history and disease duration between the MN-166 and placebo groups at baseline. Plans are in place to mitigate the risk of this occurring again in the upcoming Phase 2b/3 study (NCT04057898)
- The efficacy of MN-166 is expected to be more robust in patients with a short ALS history.

Watanabe H, Atsuta N, Hirakawa A et al. A rapid functional decline type of amyotrophic lateral sclerosis is linked to low expression of TTN. J Neurol Neurosurg Psychiatry 2016