Effect of Ibudilast on Neurofilament-light Chain in Progressive MS: Analysis from a Phase II Trial

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On behalf of N102 SPRINT MS Investigators

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Background

NL is a candidate biomarker of treatment response in multiple sclerosis (MS) clinical trials. NL was evaluated in several MS trials of anti-inflammatory therapies where the anti-inflammatory therapies were shown to decrease NL levels. However, the utility of NL as a biomarker in MS trials of non-anti-inflammatory therapies has not been reported previously.

Ibudilast is a small, brain-penetrating molecule that inhibits several cyclic nucleotide phosphodiesterases, macrophage migration inhibitory factor, and toll-like receptor 4. In a phase II trial in relapsing MS, ibudilast did not decrease inflammation as measured by new MRI lesions, but was observed to reduce progression of brain atrophy in a dose-dependent fashion. This suggested that ibudilast may have a neuroprotective effect in the absence of an anti-inflammatory effect. This observation led to the SPRINT MS trial, which was a two-year, 256-patient, randomized, placebo-controlled phase II trial of ibudilast in progressive MS. The SPRINT MS found that ibudilast 80-100 mg/d was associated with a 48% slowing in progression of brain atrophy over two years. The SPRINT MS trial provides an ideal setting to evaluate the performance of NL.

Objective

To report the effect of ibudilast on serum and CSF neurofilament light (NFL) from the phase II trial of ibudilast in progressive MS.

Methods

Serum samples were collected at screening, 8, 48, and 96 weeks. In an optional sub-study, 75 patients consented to CSF sampling, which was collected at screening, 48, and 96 weeks. NL was assayed using the SIMOA immunoassay. Analysis followed that of Kuhle, et al (Neurology 2019) using mixed model for repeated measures with log (baseline NfL) as the response variable and adjusted for treatment, age and log baseline NL for serum NL, and adjusted for treatment and age for CSF NL. The model further included visit-by-treatment and visit-by-log baseline NL interactions for serum NL, and only visit-by-treatment interactions for CSF NL, using an unstructured covariance matrix. Analysis was according to intent-to-treat (ITT) and included all available values in the statistical analysis.

Because active inflammation and other brain tissue injury can cause elevations of NL and thus may confound the results, an effort was made to control for this confounding: Censored Cohort 1 excluded time points:

a) at or after onset of neurologic serious adverse events (SAEs), or
b) within 6 months after a clinical relapse, or
c) when MRI showed any new or enlarging T2 lesions.

Since no MRI was obtained at week 8, all data from week 8 was excluded. Censored Cohort 2 was the same as Cohort 1 except exclusion c) was relaxed to only exclude time points when MRI showed >3 new or enlarging T2 lesions.

Results

Full Cohort

Over the course of the study, NL increased in the overall study population (p<0.001). No between-group difference in NL was observed in either serum (P=0.76) or CSF (P=0.46).

Censored Cohorts

Comparison of the most restrictive censoring (any new/enlarging T2 lesions) to a less restrictive (>3 new/enlarging T2 lesions) found only modest advantage to the most restrictive censoring, but loss of 11% of subjects from both serum and CSF datasets (Table). In neither Cohort 1 nor Cohort 2 was between-group difference in NL observed in either serum (Cohort 1 p = 0.93; Cohort 2 p = 0.69) or CSF (Cohort 1 p = 0.48; Cohort 2 p = 0.24).

Conclusions

In a phase II trial in progressive MS, ibudilast treatment was not associated with a change in either serum or CSF NL. CNS injury from serious adverse events, relapses, and new lesions on MRI were associated with increased neurofilament levels. Concurrent CNS injury may confound the use of NL to measure potential neuroprotection from a non-anti-inflammatory therapy.

Acknowledgements:

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Disclosure:

Full Cohort

<table>
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<tr>
<th>Serum</th>
<th>Censored</th>
<th>Placebo</th>
<th>Budilast</th>
<th>Placebo</th>
<th>Budilast</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cohort 1</td>
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<td>29.7 ±119</td>
<td>110.8 ± 92</td>
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<tr>
<td>Cohort 2</td>
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<td>27.7 ±103</td>
<td>109.4 ± 97</td>
<td>127.5 ±218</td>
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Censored Cohorts (cont.)

<table>
<thead>
<tr>
<th>Serum</th>
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<th>Placebo</th>
<th>Budilast</th>
<th>Placebo</th>
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<td>27.7 ±103</td>
<td>109.4 ± 97</td>
<td>127.5 ±218</td>
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