**Effect of ibudilast on macular measures in progressive MS: OCT analysis from the SPRINT-MS Trial**

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### Objective

To study the effect of ibudilast on macular measures from the SPRINT-MS phase II trial of ibudilast in progressive MS.

### Background

- Macular volume loss and thinning of the ganglion cell/inner plexiform layer (GCIP) are both measures of tissue injury in MS and can be measured by optical coherence tomography (OCT).
- Ibudilast 100 mg/d was found to slow the progression of brain atrophy in SPRINT-MS, a 255-patient randomized, placebo-controlled 96-week phase II trial in progressive MS.
- Study population for SPRINT-MS was a mix of primary (53%) and secondary progressive (47%) MS, average age 56 years and median EDDS=6.0 at baseline, as has been described.\(^1,2\)
- Peripapillary RNFL was a secondary outcome measure which slowed RNFL thinning in ibudilast-treated patients, although not statistically significant:
  - 0.3054μm less pRNFL thinning over 48 weeks in ibudilast-treated patients, 95% CI -0.1786 to 0.7893.
- For this analysis, we evaluated the effect of ibudilast on macular volume loss in SPRINT-MS.

### Design/Methods:

- Patients underwent OCT at baseline and every 24 weeks using either Cirrus (n=183) or Spectralis (n=61) spectral domain devices, based on the available at each study site.
- A central reading center [The Digital OCT Reading Center (DOCTR) at Cleveland Clinic] with two independent certified graders performed quality assurance and entered OCT data into the study database according to established protocols.
- Macular volume was measured from both Cirrus and Spectralis devices, but was analyzed independently due to differences in scan acquisition and measurement between the two technologies.\(^2\)
- GCIP thickness was analyzed from scans acquired on Cirrus devices.
- Study scheme is depicted below with OCT time points:

<table>
<thead>
<tr>
<th>Baseline</th>
<th>Week 24</th>
<th>Week 48</th>
<th>Week 72</th>
<th>Week 96</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ibudilast</td>
<td>OCT</td>
<td>OCT</td>
<td>OCT</td>
<td>OCT</td>
</tr>
<tr>
<td>Placebo</td>
<td>OCT</td>
<td>OCT</td>
<td>OCT</td>
<td>OCT</td>
</tr>
</tbody>
</table>

- All available data and time points were included in a modified intent-to-treat analysis and the rates of change between the trial groups over time were compared using linear mixed models.

### Results:

- Macular measures were similar between ibudilast and placebo groups at baseline:

<table>
<thead>
<tr>
<th>Treatment Group</th>
<th>Estimated Annual Rate of Change (95% CI)</th>
<th>P-value for Difference in Rate of Change</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ibudilast</td>
<td>0.005 (-0.027, 0.017)</td>
<td>0.44</td>
</tr>
<tr>
<td>Placebo</td>
<td>-0.037 (-0.058, 0.015)</td>
<td></td>
</tr>
</tbody>
</table>

- In patients followed with Spectralis OCT, the estimated rate of macular volume change was slower for ibudilast than placebo:

<table>
<thead>
<tr>
<th>Treatment Group</th>
<th>Estimated Annual Rate of Change (95% CI)</th>
<th>P-value for Difference in Rate of Change</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ibudilast</td>
<td>-0.002 (-0.023, 0.002)</td>
<td>0.173</td>
</tr>
<tr>
<td>Placebo</td>
<td>-0.021 (-0.041, 0.000)</td>
<td></td>
</tr>
</tbody>
</table>

### Conclusions:

- Annual macular volume loss using Spectralis OCT over 96 weeks was slower with ibudilast compared to placebo.
- Cirrus OCT demonstrated favorable changes towards reduced macular volume loss and GCIP layer thinning.
- These OCT results, together with the positive effect on brain atrophy support the potential benefit of ibudilast in progressive MS.
- The OCT analyses lend further support for a phase III trial to determine clinical benefit of ibudilast in progressive MS.
- In the future, a platform-agnostic analysis be helpful to analyze macular volume and GCIP aggregated across both imaging platforms.

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### Acknowledgments & References:

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