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

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Objective

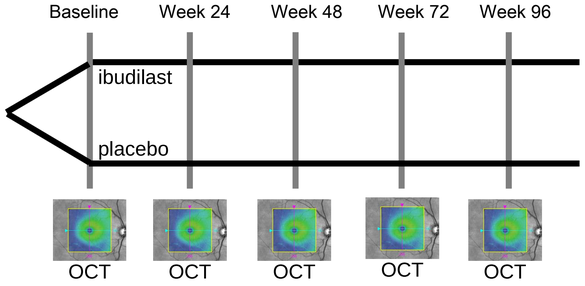
To study the effect of ibudilast on macular measures from the SPRINT-MS phase II trial of ibudilast in progressive MS.

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 EDSS=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:
  - 0.3054uM 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:



- 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:

	ibudilast mean (SD) N	placebo mean (SD) N
Baseline MV Spectralis	8.26 mm³ (0.46) N=30	8.12 mm³ (0.46) N=30
Baseline MV Cirrus	9.70 mm³ (0.54) N=90	9.59 mm³ (0.58) N=91
Baseline GCIP Cirrus	71.69 uM (8.98) N=90	68.89 uM (9.71) N=90

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

MACULAR VOLUME CHANGE - SPECTRALIS SITES

Treatment group	Estimated annual rate of MV change (95% CI)	P-value for difference in rate of change
Ibudilast	-0.005 (-0.027, 0.017)	**0.044**
Placebo	-0.037 (-0.058, -0.015)	

- In patients followed with Cirrus OCT, the estimated rate of macular volume change showed a numerical slowing with ibudilast, but wasn't significant:

MACULAR VOLUME CHANGE - CIRRUS SITES

Treatment group	Estimated annual rate of MV change (95% CI)	P-value for difference in rate of change
Ibudilast	-0.000 (-0.022, 0.021)	0.173
Placebo	-0.021 (-0.041, -0.000)	

- In patients followed with Cirrus OCT, the rate of change of GCIP showed a numerical slowing with ibudilast, but wasn't significant.

GCIP THICKNESS – CIRRUS SITES

Treatment group	Estimated annual rate of GCIP change (95% CI)	P-value for difference in rate of change
Ibudilast	-0.489 (-0.913, -0.065)	0.118
Placebo	-0.959 (-1.368, -0.550)	

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.

Acknowledgments & References:

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1. Fox RJ et al. N Engl J Med 2018; 379:846-855.
2. Fox RJ et al. Contemp Clin Trials 2016; 50:166-77.
3. Warner CV et al. PLoS ONE 2011; 6(8): e22947.