Ozanimod (RPC1063) reduces the plasma biomarker neurofilament light chain in preclinical rodent models of multiple sclerosis

Short Title: Ozanimod reduces neurofilament light chain

K. R. Taylor Meadows, F. L. Scott, C. Villescaz, B. Clemons, C. Lopez, S. Sawa-Ballweber, K. Dines, G. J. Opiteck

Receptos, a wholly owned subsidiary of Celgene, San Diego, California, United States

Background: Ozanimod (RPC1063) selectively targets sphingosine 1-phosphate receptor 1 ($S1P_{R1}$) and 5 ($S1P_{R5}$) and demonstrates therapeutic benefit in relapsing multiple sclerosis (RMS) clinical trials. Ozanimod modulation of $S1P_{R1}$ on lymphocytes may disrupt the inflammatory cascade of MS. Furthermore, ozanimod penetrates the blood brain barrier and potentially promotes neuroprotection through modulation of $S1P_{R1}$ and $S1P_{R5}$ on neural cells. Neurofilament light chain (NfL) is released into the cerebrospinal fluid and serum/plasma following axonal injury and neuronal damage and may serve as a biomarker for neurological damage in RMS.

Methods: Plasma NfL concentration was measured in experimental autoimmune encephalomyelitis (EAE) and cuprizone-induced demyelination mouse models using Simoa technology (Quanterix, Lexington, MA). In EAE, mice were therapeutically dosed with ozanimod for 14 days, then spinal cords were assessed for inflammation by hematoxylin and eosin staining and demyelination by Luxol Fast Blue at termination. In the cuprizone model, mice were treated with an ozanimod surrogate (RP-101074) for six weeks concurrently with cuprizone and corpus callosum sections at termination were stained with SMI-32 to evaluate neuronal breaks.

Results: Plasma NfL was significantly elevated in EAE and cuprizone-treated mice over naïve controls. Elevated plasma NfL levels correlated with spinal cord inflammation and demyelination in EAE and with neuronal breaks in the corpus callosum of mice treated with cuprizone. Ozanimod treatment in EAE significantly reduced plasma NfL levels, correlating with a significant reduction in clinical scores, spinal cord inflammation, and demyelination. Mice treated with RP-101074 in the cuprizone model had significantly reduced plasma NfL and neuronal breaks.

Conclusion: Plasma NfL served as a biomarker indicative of CNS injury, inflammation, and demyelination in EAE and cuprizone-induced demyelination. Ozanimod treatment significantly reduced plasma NfL in both models. These effects indicate a potential positive and direct CNS effect of ozanimod.

Disclosure: K. R. Taylor Meadows, Shareholder: Celgene. F. L. Scott, Shareholder: Celgene. C. Villescaz, Shareholder: Celgene. B. Clemons, Shareholder: Celgene. C. Lopez, Shareholder: Celgene. S. Sawa-Ballweber, Shareholder: Celgene. K. Dines, Shareholder: Celgene. G. J. Opiteck, Shareholder: Celgene.