Ozanimod (RPC1063) Reduces the Plasma Biomarker Neurofilament Light Chain in Preclinical Rodent Models of Multiple Sclerosis

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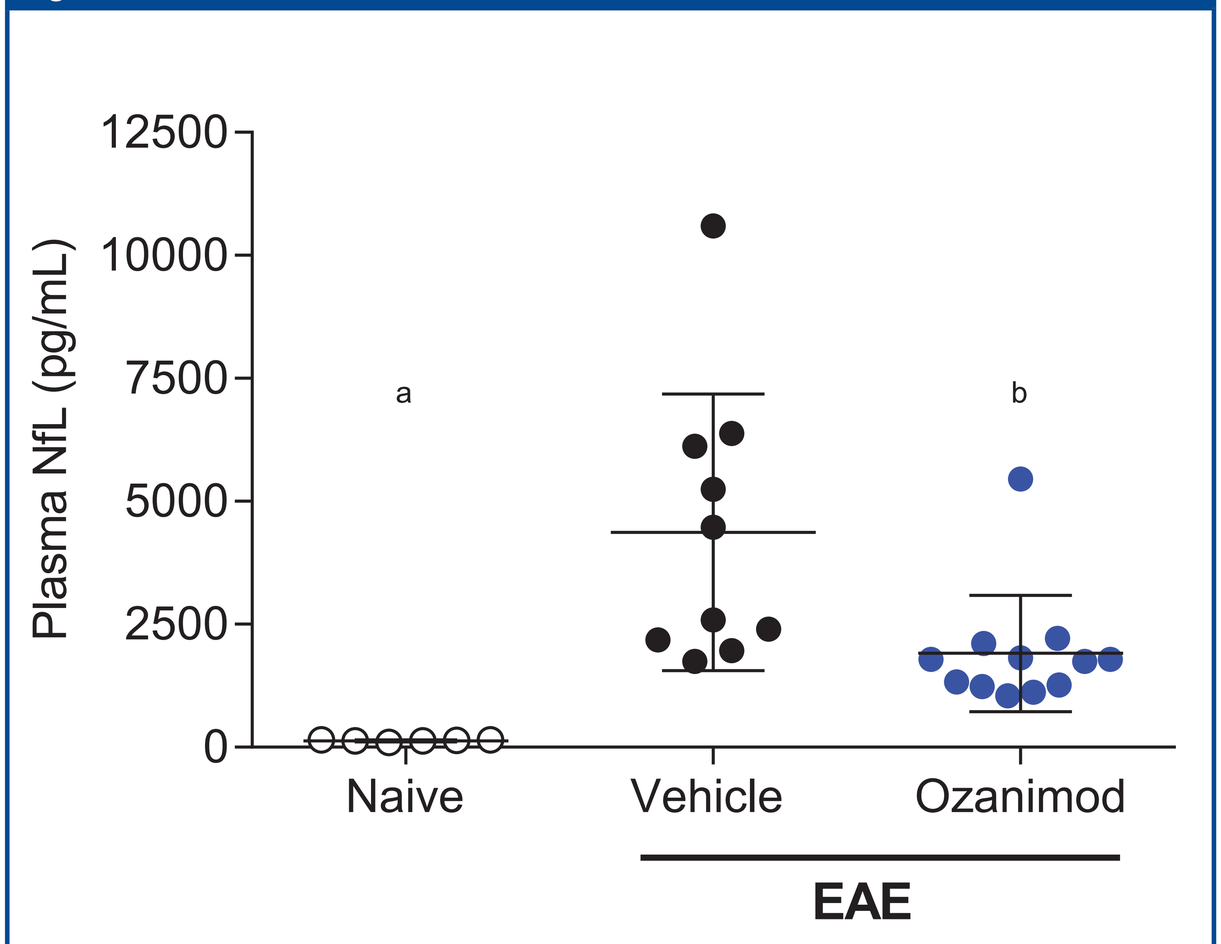
INTRODUCTION

- Ozanimod (RPC1063) selectively targets sphingosine 1-phosphate ($S1P_{R1}$) and $S1P_{R5}$ and has shown therapeutic benefit in clinical trials of relapsing multiple sclerosis (RMS) and ulcerative colitis[1,2]
- Ozanimod is an oral, once-daily immunomodulator that selectively targets $S1P_{R1}$ and $S1P_{R5}$ to mitigate autoimmune responses, while potentially maintaining a level of immune surveillance and allowing rapid recovery of lymphocytes following treatment cessation[3,4]
- In addition, ozanimod has been shown preclinically to penetrate the central nervous system (CNS), where its effects on $S1P_{R1}$ and $S1P_{R5}$ expressed on specific cells may confer neuroprotective benefits[4–9]
- Neurofilament light chain (NfL) is released into the cerebrospinal fluid and serum/plasma following neuronal injury and degeneration[10]
- It may serve as a biomarker for monitoring neurological damage in RMS[11,12]

Figure 1. Ozanimod Decreases Plasma NfL in the EAE Mouse Model of MS



EAE, experimental autoimmune encephalomyelitis; MS, multiple sclerosis; NfL, neurofilament light chain.
[a]P<0.001, [b]P<0.01 versus vehicle-treated animals.

RESULTS

- Plasma NfL was significantly elevated in EAE (Figure 1) and cuprizone-treated mice (Figure 2) over naive 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 and spinal cord inflammation and demyelination
- Mice treated with RP-101074 in the cuprizone model had significantly reduced plasma NfL and neuronal breaks, supportive of a neuroprotective effect

DISCLOSURES

All authors: Shareholder, Celgene Corporation.

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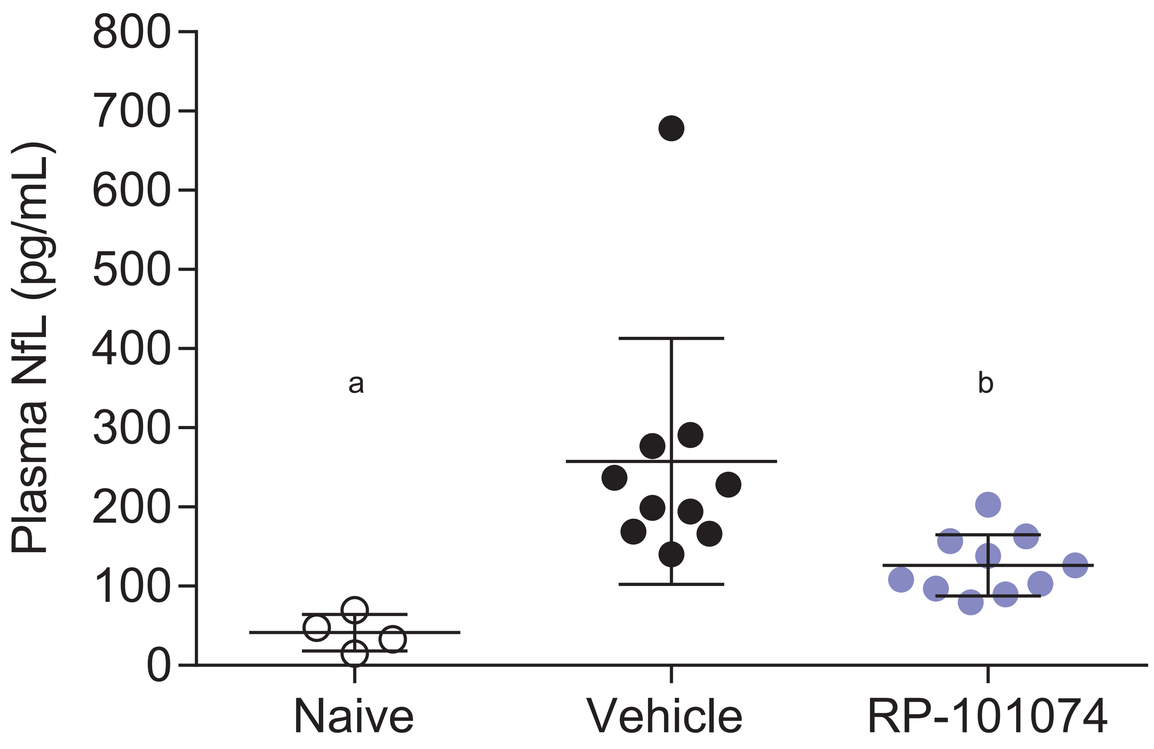
DISCUSSION

- Plasma NfL was significantly elevated in EAE mice and in the cuprizone-treated mice compared with naive, non-diseased animals
- Elevated plasma NfL correlated with clinical scores and spinal cord inflammation and demyelination in EAE, as well as with neuronal breaks in the cuprizone model
- In both of these preclinical studies, plasma NfL served as a biomarker indicative of CNS injury, inflammation, and demyelination
- These observed effects indicate a potential positive and direct CNS effect of ozanimod

METHODS

- The concentration of NfL was measured in the plasma of experimental autoimmune encephalomyelitis (EAE) and cuprizone-induced demyelination mouse models
- Blood was isolated from mice via terminal cardiac puncture, and plasma NfL was measured at Quanterix (Lexington, MA) using the Simoa technology platform
- In EAE, mice were therapeutically dosed with ozanimod for 14 days, and then spinal cords were assessed at termination 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 6 weeks concurrently with cuprizone, and corpus callosum sections at termination were stained with the anti-neurofilament H mouse monoclonal antibody (SMI-32) to evaluate neuronal breaks

Figure 2. The Ozanimod Surrogate RP-101074 Reduces Plasma NfL in the Cuprizone-induced Demyelination Mouse Model



NfL, neurofilament light chain.
[a]P<0.01, [b]P<0.05, versus vehicle-treated animals.

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