# Identification of neurorestorative biomarkers in patients with relapsing forms of multiple sclerosis

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**The Methodological Question Being Addressed:** What biomarkers suggesting neurorestorative antibody target engagement can be identified in multiple sclerosis patients?

**Introduction (Aims):** Elezanumab is a fully humanized monoclonal antibody directed against repulsive guidance molecule A (RGMa). Studies in patients with multiple sclerosis (MS) demonstrate RGMa upregulation, which inhibits axonal growth and myelination, oligodendroglial regeneration and functional recovery after trauma or inflammation. Elezanumab is being developed as a neurorestorative treatment, to be administered with immunomodulator therapy and designed to promote recovery of neurophysical, sensory and cognitive disability. The objective of this analysis was to demonstrate biomarker evidence of target engagement. This will serve two purposes: 1) ensure adequate testing of the hypothesis, and 2) enable possible early termination of efficacy trials.

**Methods:** For each of 3 dose levels studied serially, patients were randomized to receive either active treatment (n=5) or placebo (n=2). A total of 20 patients with relapsing remitting or secondary progressive MS were enrolled. Elezanumab doses were given intravenously every 4 weeks for a total of 4 doses, with a loading dose of double the maintenance dose given on Day 1. The dose levels were 150 mg, 600 mg, and 1800 mg. Serum and cerebral spinal fluid samples for biomarker analysis were collected at baseline and throughout the trial. Magnetic resonance imaging (MRI) was also conducted.

**Results:** Free soluble RGMa decreased with increasing levels of elezanumab in cerebral spinal fluid (CSF). Maximum reduction was approximately 50% from baseline. Total RGMa (both free and antibody-bound) levels increased linearly with CSF elezanumab exposure. CSF interleukin-10 (IL-10) also increased in the CSF following elezanumab administration compared with placebo. A dose-response reduction was observed with neurofilament light (NF-L). T2 lesion volume was not impacted by elezanumab therapy.

**Conclusions:** Evidence of target engagement was demonstrated with effects on IL-10 and NF-L, which are mechanistically plausible markers of inflammation and neurodegeneration. These will be useful measures of target engagement in later stage studies. Evidence of target binding was demonstrated with reduction in soluble RGMa. No effect on traditional MRI was demonstrated, though myelin specific imaging may be informative in subsequent development.

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