A Phase 1, Multiple-dose Study of Elezanumab (ABT-555) in Patients with Relapsing Forms of Multiple Sclerosis

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Objective: The current study evaluated multiple doses of elezanumab to determine its safety and tolerability in patients with relapsing forms of MS.

Background: 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 treatment promoted axon regeneration, neuroprotection, remyelination, and immune modulation in several MS-relevant preclinical models. Elezanumab was previously well-tolerated as a single dose to healthy volunteers.

Design/Methods:
In this phase 1, double-blind, placebo-controlled, randomized, escalating multiple-dose 29-week study, patients were randomized into 3 treatment groups (150 mg, 600 mg, and 1800 mg elezanumab) and 1 placebo group. Of the 20 patients enrolled, 18 had relapsing-remitting MS and 2 had secondary progressive MS. 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. Assessments included adverse events (AEs), cerebral spinal fluid (CSF) and plasma biomarker analysis, and Expanded Disability Status Score (EDSS). Subsequently, magnetic resonance imaging and serum pharmacokinetics data will be reported.
Results:
The most common AE was headache (25% of all patients). Free soluble RGMa decreased with increasing levels of elezanumab in CSF, while total RGMa (both free and antibody-bound) increased linearly with CSF elezanumab exposure. Interleukin-10 also increased in the CSF following elezanumab administration compared with placebo. Through the end of the follow-up period, the majority of patients receiving elezanumab did not experience a clinically significant worsening or improvement in EDSS scores.
Conclusions:
Elezanumab was well-tolerated and did not consistently result in symptom worsening in patients who received multiple doses of up to 1800 mg. Additional long-term studies are required to elucidate elezanumab efficacy in a more robust patient population.