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**Title:** GNBAC1 shows efficacy on MRI measures of neurodegeneration in relapsing-remitting MS patients over 48 weeks.

**Background:** Human endogenous retroviruses (HERVs), resulting from germline, retroviral DNA insertions, represent approximately 8% of the human genome. Pathogenic HERV-W envelope protein (pHERV-W env), a potent Toll-like receptor 4 (TLR4) agonist, activates microglia and inhibits oligodendrocyte precursor cell (OPC) maturation, both *in vitro* and in animal models of MS. The humanised IgG4 monoclonal antibody GNBAC1 inhibits pHERV-W env mediated pathogenicity in preclinical models of MS.

**Methods:** GNC-003 (CHANGE-MS), a European, Phase IIb study, randomised 270 relapsing remitting multiple sclerosis (RRMS) patients 1:1:1:1 to GNBAC1 (6, 12 or 18 mg/kg) or placebo, via monthly, IV infusion, for 24 weeks (Period 1). At Week 24, placebo patients were re-randomised 1:1:1, to active GNBAC1 for another 24 weeks (Period 2). Patients, investigators, site staff, blinded CRO staff and Central MRI Reading Center remained blinded to treatment assignment throughout. Original randomization groups were maintained for pre-specified, Week 48 comparative analyses.

**Results:** Week 24 data were previously presented. Over 90% of randomized patients completed Week 48. Treatment with GNBAC1 (18mg/kg) resulted in a 63% relative reduction in the number of new T1 hypointense lesions at week 48. Relative reductions in atrophy rates over 48 weeks were: whole brain = 29%, cerebral cortex = 31% and thalamus = 72% versus placebo (comparator group). Dose-response relationships, based on Spearman Rank-Order Correlations, were observed for most atrophy measures. Post-hoc analyses showed consistent efficacy in the sub-population of non-active patients (without gadolinium-enhanced lesions at baseline). GNBAC1 18 mg/kg maintained myelin integrity through Week 48, as measured by Magnetization Transfer Ratio (MTR), in normal-appearing white matter and cerebral cortex.

#### **Conclusion:**

At Week 48, GNBAC1 18 mg/kg showed consistent efficacy across MRI measures of neurodegeneration. These results confirm preclinical observations of the neuroprotective effects of pHERV-W env blockade, and suggest the potential for GNBAC1 to slow disability progression in MS patients.

#### **Disclosures**

*François Curtin and Robert Glanzman are employees of GeNeuro S.A., Hans-Martin Schneble and Estelle Lambert are employees of Servier.*