GNbAC1 Provides Evidence for Neuroprotection in RRMS Patients

(Week 48 Data from CHANGE-MS; *Clinical trial assessing the HERV-W Env antagonist GNbAC1 for Efficacy in MS*)

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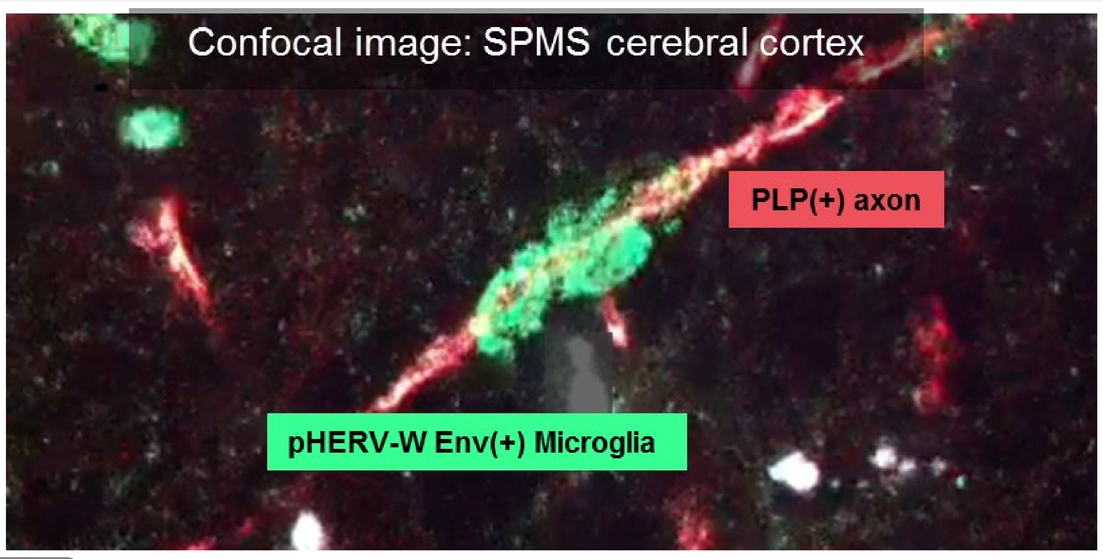
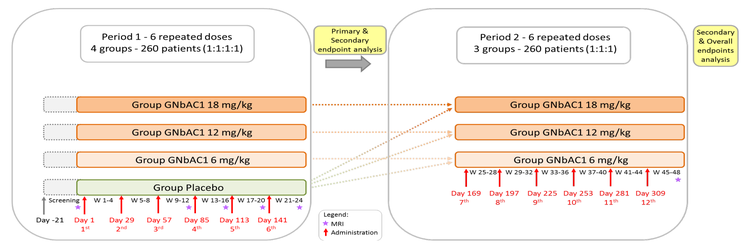
Background

Human endogenous retroviruses (HERVs) result from ancestral, germline, retroviral DNA insertions, representing 8% of the human genome. A pathogenic member of the HERV-W family [pHERV-W; formally, the multiple sclerosis-associated retrovirus (MSRV)] may be tansactivated by environmental factors such as Epstein-Barr Virus to generate pathogenic viral products, including the envelope protein [(pHERV-W Env); a potent agonist of Toll-like Receptor 4 (TLR4)]. The humanised IgG4-κ monoclonal antibody (mAb) GNbAC1 targets and blocks pHERV-W Env, inhibiting TLR4-mediated pathogenicity, including: activation of macrophages and microglia into pro-inflammatory phenotypes and direct inhibition of remyelination via TLR4 expressed on oligodendrocyte precursor cells (OPCs) during maturation. Here we present the Week-48 data from the first efficacy study ever performed of a HERV-specific directed therapy in multiple sclerosis.



Study Overview

Methods: This international, Phase IIb study randomized 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-randomized 1:1:1, to active GNbAC1 for another 24 weeks (Period 2). For Period 2, patients, investigators, site and CRO staff remained blinded to original and re-randomized treatment assignment. The MRI Central Reading Center remained blinded throughout. Original randomization groups were maintained for pre-specified, Week 48 comparative analyses.

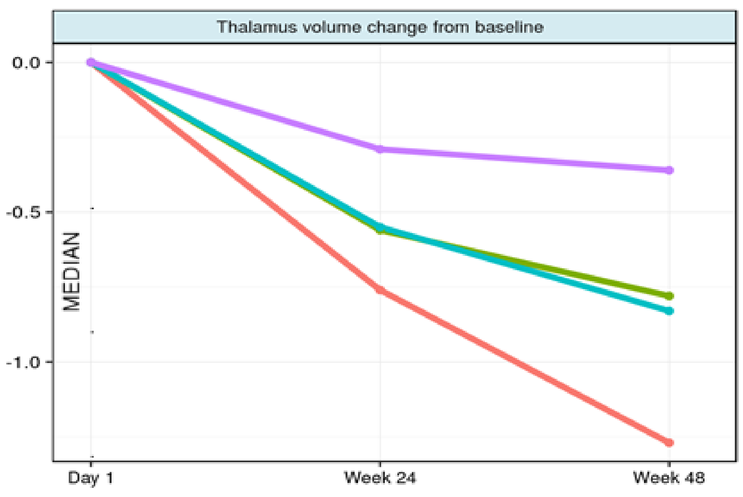


Results Week 24 data were previously presented. Over 90% of randomized patients were available for analysis at Week 48. At Week 48 GNbAC1 (18mg/kg) showed beneficial effects on accepted markers of neurodegeneration in comparison with the original placebo (Comparator) group. Reductions were seen in the number of T1 hypointense lesions and CNS structural atrophy (whole brain, cerebral cortex, thalamus and deep grey nuclei). Statistically significant dose responses, based on Spearman rank correlation coefficient analyses, were observed for most atrophy endpoints. Benefits in Magnetization Transfer Ratio (MTR) were consistent with Week 24 findings with stablisation of median MTR values in Normal Appearing White Matter (NAWM) and Cerebral Cortex (CC). No significant safety issues were identified and GNbAC1 18 mg/kg was well tolerated and pharmacokinetics were dose-linear.

Week-48 Neurodegeneration Outcomes

Reduced CNS volume loss versus the Comparator Group

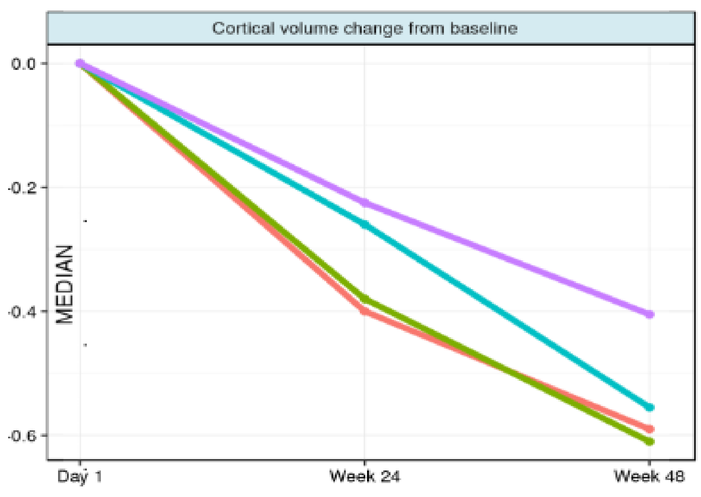
Thalamus



Group	Median % reduction at week 48	Relative reduction Median volume
Comparator	-1.27	
18mg/kg	-0.36	**72%**

Dose response* p=0.014

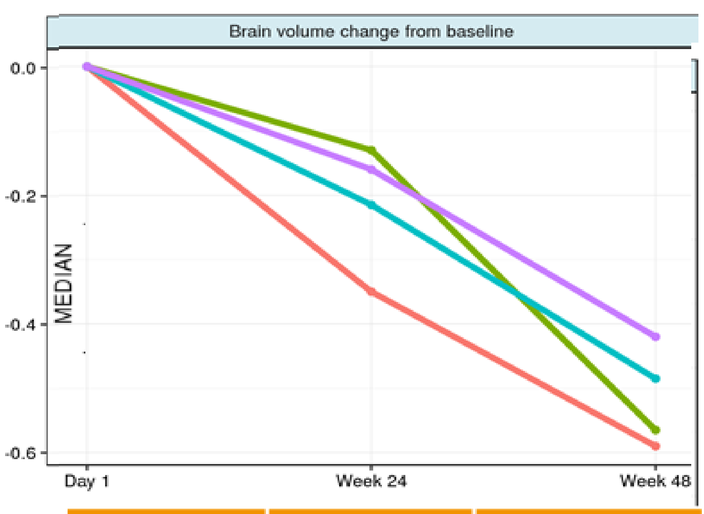
Cerebral cortex



Group	Median % reduction at week 48	Relative reduction median volume
Comparator	-0.59	
18mg/kg	-0.41	**31%**

Dose response* p=0.045

Whole brain



Group	Median % reduction at week 48	Relative reduction median volume
Comparator	-0.59	
18mg/kg	-0.42	**29%**

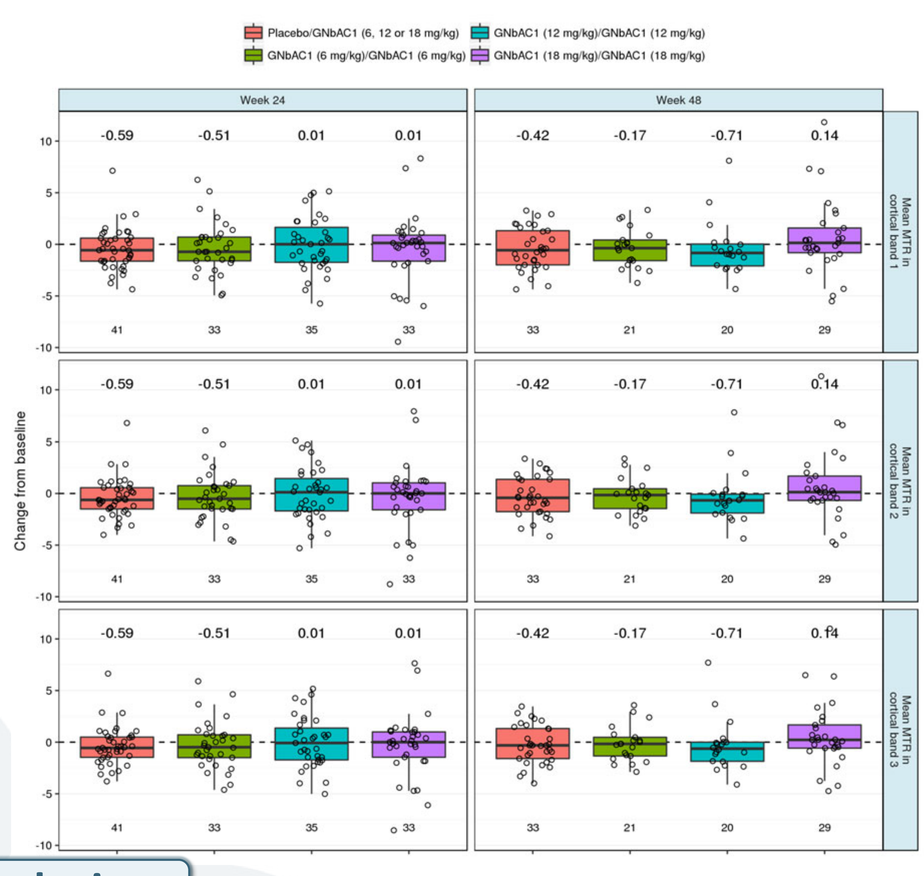
Dose response* p=0.079

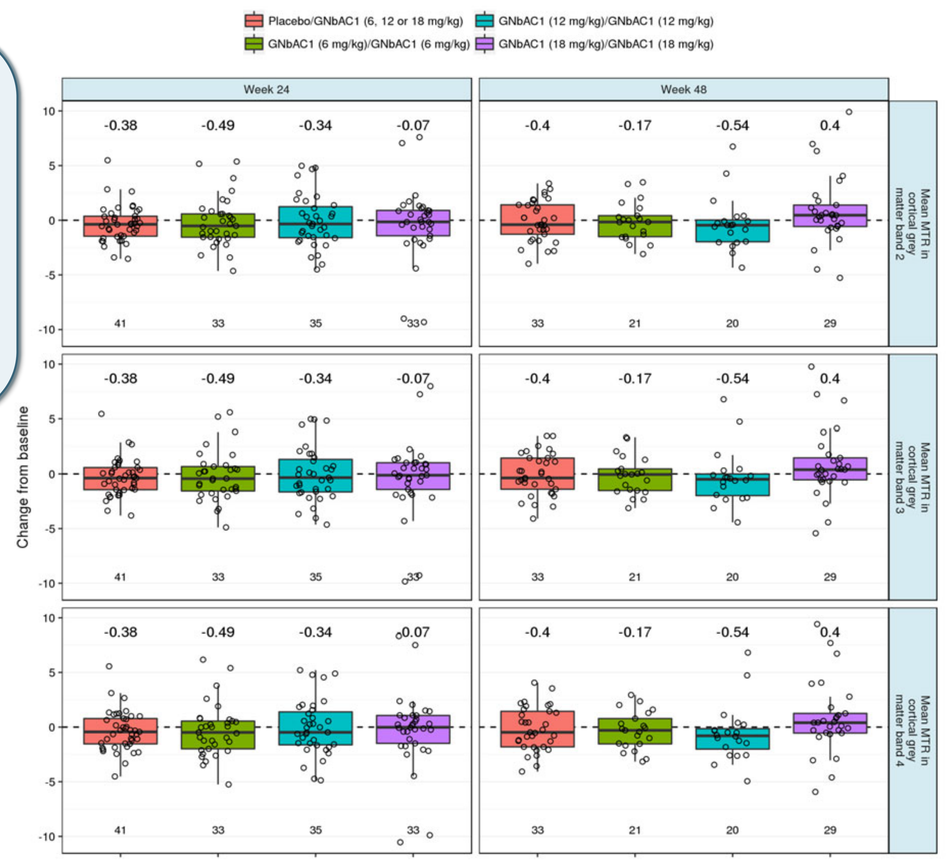
Placebo/GNbAC1 (6, 12 or 18 mg/kg) | GNbAC1 (12 mg/kg)/GNbAC1 (12 mg/kg)
GNbAC1 (6 mg/kg)/GNbAC1 (6 mg/kg) | GNbAC1 (18 mg/kg)/GNbAC1 (18 mg/kg)

* Dose response analyzed by Spearman Rank Correlation Coefficient

Week-48 Outcomes

Stabilization of median MTR values in NAWM and CC Versus Comparator





References

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Conclusion

This study provides evidence for dose-dependent effects on MRI markers of neurodegeneration with GNbAC1 in RRMS. Given preclinical findings showing pHERV-W env activation of microglia and direct inhibition of OPC maturation, these results demonstrate the potential for this target in MS. Neutralizing pHERV-W env may help to prevent neurodegeneration, a major unmet need in MS therapy. As the maximum dose tested appeared to be most effective and no safety concerns emerged, higher doses may be considered in future studies. GNbAC1 should be studied as an adjunctive treatment for patients with active, relapsing MS and, potentially, a monotherapy for patients with inactive, progressive MS.

Disclosure of Potential Conflicts of Interest: RG, FC and HPo are employees of GeNeuro SA; HMS and EL are employees of Servier.