GNbAC1, a humanized IgG4 antibody neutralizing HERV-W Envelope protein; pre-clinical development and Results from Phase I/IIa clinical trials in Healthy volunteers and in MS patients

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ABSTRACT

Monoclonal antibodies (mAbs) play an increasing important role in the therapeutic armamentarium against multiple sclerosis (MS). After identification of precursor murine and chimeric versions, GNbAC1, a humanized IgG4 mAb, was developed to target the multiple sclerosis associated retrovirus envelope (MSRV-Env) protein, an upstream factor in the pathophysiology of MS. We present the preclinical and early clinical development results of GNbAC1. The specificity of GNbAC1 for its endogenous retroviral target is described. Efficacy of GNbAC1 were assessed in MSRV-Env induced experimental allergic encephalitis (EAE), an animal model of MS. Because the target MSRV-Env is not expressed in animals, no relevant animal model exists for a proper in vivo toxicological program. An off-target 2-week toxicity study in mice was thus performed, and it showed an absence of safety risk. Additional in vitro analyses confirmed specificity and an absence of complement or antibody-dependent cytotoxicity. The first-in-man clinical study in 33 healthy subjects and a long-term clinical study in 10 MS patients showed that GNbAC1 is well tolerated in healthy subjects as well as in MS patients, without induction of immunogenicity. Moreover GNbAC1 induces a pharmacodynamic response on MSRV biomarkers. These initial results suggest that the mAb GNbAC1 could be a safe long-term treatment for patients with MS with a unique therapeutic mechanism of action.