

Title: Antigen-specific immunomodulation in multiple sclerosis patients treated with MBP encoding DNA plasmid (BHT-3009) alone or combined with atorvastatin

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Objective: To assess immunomodulation by BHT-3009 in MS patients

Background: We have previously shown that DNA plasmids induce antigen-specific immunomodulation in animal models of autoimmune disease. We have begun clinical testing of BHT-3009, a DNA plasmid that expresses full-length human MBP.

Design/methods: We are conducting a placebo-controlled 30 patient phase I/II trial of BHT-3009 alone or in combination with atorvastatin in relapsing MS patients. Within this trial we are measuring several immune parameters including CFSE based antigen-specific T cell proliferation and intracellular cytokine production by peripheral blood mononuclear cells.

Results: Twenty patients have completed treatment and assays are ongoing. Data from the CFSE assay on patients in the first two cohorts demonstrate antigen-specific reduction in MBP reactive T cells by week 9 of treatment in three out of four patients. In the first patient, the proliferation of MBP83-99 reactive IFN- γ positive cells decreased from 25.9% to 1.2 %. In a second patient, the proliferation of MBP83-99 reactive IFN- γ positive cells decreased from 13.3% to 5.4%. In the third patient, the proliferation of whole MBP reactive IFN- γ positive cells decreased from 2.27% to 0.79%. In all three of these patients the proliferation to tetanus toxoid did not decrease, pointing to antigen specificity of the in vivo effect. In a fourth patient, there was no change in either the MBP83-99, whole MBP or tetanus proliferative responses. Analysis of the third cohort of 10 patients will be complete at the beginning of 2006.

Conclusion: To our knowledge this is the first clinical trial of a DNA plasmid for antigen-specific immunotherapy of any autoimmune disease. The data on three out of four patients where immune assay results are available suggest that BHT-3009 may decrease the in vivo proliferative activity and IFN- γ responses of MBP specific T cells expressing Th1 cytokines associated with MS lesion formation.