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Phase I/II trial of a MBP encoding DNA plasmid (BHT-3009) alone or combined with atorvastatin for treatment of multiple sclerosis

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Objective: To assess safety and immune modulation 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 30 patient, randomized, double-blind, placebo-controlled trial in relapsing MS patients. The primary outcome measures are safety and changes in immune response. BHT-3009 is injected intramuscularly in weeks 1, 3, 5 and 9 and atorvastatin (80 mg) is taken daily for 13 weeks. Three dose levels of BHT-3009 are being tested (0.5 mg, 1.5 mg and 3.0 mg). 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: All thirty patients have been randomized. To date, the twenty patients in cohorts 1 (0.5 mg) and 2 (1.5 mg) have all completed treatment. There were 22 treatment-related adverse events (AEs), all of which were mild/moderate: 12 on placebo and 10 on BHT-3009 arms. Mean blood levels of BHT-3009 plasmid (per 10 uL) one day after injection were 2973 copies for cohort 1 and 5144 copies for cohort 2.

Data from the CFSE assay on four patients from two centers who ran this assay in the first two cohorts demonstrate antigen-specific reduction in MBP reactive T cells by week 9 of treatment in three of them. 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 following BHT-3009 treatment. In a fourth patient, there was no change in either the MBP83-99, whole MBP or tetanus proliferative responses. Analysis of the ten patients in cohort three will be complete in mid-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 indicate that BHT-3009 is safe and may suppress immune responses in an antigen-specific manner. Based on this, initiation of a 250 patient phase 2 trial in RR-MS has begun.