

Title: A Phase 1 Clinical Trial of CERE-110 (AAV-NGF) Gene Delivery in Alzheimers Disease

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Objective: To determine safety, tolerability and preliminary efficacy of in vivo Nerve Growth Factor (AAV-NGF) gene delivery in Alzheimers disease (AD).

Background: In animals, NGF: 1) prevents cholinergic degeneration caused by injury, amyloid expression, excitotoxicity, or aging, 2) augments cholinergic neuron function, and 3) improves memory. A previous Phase 1 trial of cellular gene delivery in AD reported that NGF was safe, increased glucose metabolism and may have reduced cognitive decline (Tuszynski et al., Nat Med 2005).

Design/Methods: This trial examined the safety of adeno-associated viral (AAV) in vivo NGF gene delivery in six subjects with mild-to-moderate Probable AD. Subjects with MMSE scores between 16-26 received AAV-NGF (CERE-110) vector injections into two sites of each Nucleus Basalis, total vector dose 8×10^9 (n=3) or 4×10^{10} (n=3) vector genomes, using stereotactic methods. Safety, cognition and FDG PET were assessed over one year.

Results: No serious adverse events related to AAV-NGF expression occurred. One subject developed an asymptomatic subdural hygroma 3-mo post-treatment that was electively drained without complication. PET scans 6-mo post-gene delivery revealed significant increases in glucose uptake in several cortical regions. Cognitive testing one-year post treatment demonstrated a mean decline on the MMSE of 1.7 2.1 points, a decline on the ADAS-Cog of 10.2 5.6 points, an improvement on the Clinical Dementia Rating global scale of 0.2 0.2 points, and a decline on the Clinical Dementia Rating scale Sum of Boxes of 0.8 0.5 points. Two subjects had pre-treatment aphasia, rendering their scores unreliable on the ADAS-Cog; elimination of these subjects yielded an annual change on the ADAS-Cog of 1.8 2.1 points.

Conclusions/Relevance: We conclude that AAV-NGF delivery is preliminarily safe and merits further testing in controlled, Phase 2 trials.