



Presentation Abstract

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Title: Expression of neurturin following CERE-120 (AAV2-neurturin) administration to the nonhuman primate striatum: Effect of varying volume, flow rate and method of infusion

Location: Halls B-H

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Abstract: AAV2-neurturin (CERE-120) is a novel gene therapy designed to deliver the neurotrophic factor neurturin (NRTN) to the nigrostriatal system via stereotactic surgery to restore and protect degenerating dopaminergic neurons in Parkinson's disease (PD). We previously reported findings from extensive preclinical studies demonstrating the bioactivity and safety of AAV2-NRTN in rodents and nonhuman primates (for review, see Bartus et al, Parkinson's & Rel Dis, 2007), as well as the safety of CERE-120 when delivered to PD patients (Marks et al, Lancet Neurol, 2008). The present nonhuman primate study was conducted to test a number of CERE-120 dosing permutations to help select parameters to be used in a new Phase 1/2 clinical trial which is evaluating the safety and potential efficacy of CERE-120 in advanced PD patients. Both the safety of the permutations and their ability to selectively target NRTN to the putamen were evaluated. We compared the effect of: 1) varying the distribution of vector (two 5 μ L boluses along a single needle tract separated by 4mm, versus a single 10 μ L bolus); 2) infusion characteristics (continuous/automated versus pulsatile/manual infusion at mean rates of 2 and 5 μ L/min); and 3) possible interactions of different volumes and rates of infusion (comparing 10 and 50

μL infusions, at rates of 2 and 5 $\mu\text{L}/\text{min}$ each). Eighteen macaques received stereotactic injections of AAV2-NRTN (6.7×10^{12} vg/mL) targeting to each putamen. They were euthanized 8 weeks later. All brains appeared normal with no evidence of hemorrhage, edema, or other physical duress. No increase in serum NRTN antibody titers nor evidence of NRTN or CERE-120 in the CSF was detected. Volumetric analyses of NRTN immunoreactivity on coronal sections throughout the brain revealed comparable volumes of NRTN expression; i.e., with two 5 μL bolus versus single 10 μL bolus, with continuous/automated versus pulsatile/manual delivery and with 2 $\mu\text{L}/\text{min}$ versus 5 $\mu\text{L}/\text{min}$ infusions. Moreover, no evidence for significant backflow or other problems were seen under any of the conditions, including the 5 $\mu\text{L}/\text{min}$ infusion rate. A clear, two-fold increase in volume of NRTN expression was seen following 50 μL versus 10 μL CERE-120 (34×10^{10} vg versus 6.7×10^{10} vg CERE-120), with no apparent difference between 2 $\mu\text{L}/\text{min}$ versus 5 $\mu\text{L}/\text{min}$ infusion rates. Collectively, these findings provide novel information regarding the consequences of various infusion parameters when administering AAV2 vectors into brain parenchyma and useful empirical guidance for simplifying and improving specific dosing parameters for Ceregene's ongoing Phase 1/2 clinical trial examining the safety and potential efficacy of CERE-120 in PD.

Disclosures: **C.D. Herzog**, Ceregene, Inc., Employment; Ceregene, Inc., Ownership Interest; **A. Wilson**, Ceregene, Inc., Employment; Ceregene, Inc., Ownership Interest; **L. Brown**, Ceregene, Inc., Employment; Ceregene, Inc., Ownership Interest; **J. Roque**, Ceregene, Inc., Employment; Ceregene, Inc., Ownership Interest; **C. Qunitio**, Ceregene, Inc., Employment; Ceregene, Inc., Ownership Interest; **J.H. Kordower**, Ceregene, Inc., Ownership Interest; Ceregene, Inc., Consultant/Advisory Board; **R.T. Bartus**, Ceregene, Inc., Employment; Ceregene, Inc., Ownership Interest.

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