Evidence of Significant Cognitive Improvement Over Baseline in Advanced Alzheimer's Disease (AD) Patients: A Regenerative Therapeutic Strategy

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Abstract Text:

Background: Synaptogenix scientists have pioneered a regenerative therapeutic strategy designed to reduce (1.) a beta-oligomers and hyperphosphorylated tau, but importantly, (2.) also restores the AD – induced loss of synaptic networks and neurons. In pre-clinical studies (Sun and Alkon, TIPS, 2019), increased numbers of mature, mushroom spine synapses were measured with serial electron micrographs of the hippocampus with the rat spatial maze memory task, and were further significantly increased by the Bryostatin-induced activation of the PKC epsilon-BDNF cascade (Hongpaisan and Alkon, PNAS, 2007). Similarly, Bryostatin increased the numbers of mature synapses, normalized cognitive deficits, and prevented neuronal death in pre-clinical models of neurodegeneration including AD ($p<.01$, 2-tailed), stroke, Fragile X syndrome, and traumatic brain injury. Subsequently, compassionate use trials showed marked improvements in advanced AD patients (Nelson et al., JAD, 2017).

Method: Thereafter, an initial pilot (13 weeks, N=150) trial of Bryostatin to treat AD, Study #202, and a 2nd (13 weeks, N=100) pilot trial, Study #203, included identical protocols: 7 i.v. doses of 20 mcg / kg Bryostatin over 11 weeks with Placebo groups in each.

Results: Bryostatin Treatment (at Week #13) in the 1sttrial improved Severe Impairment Battery (SIB) scores over baseline (+4.5 over baseline, $p<.04$, 2-tailed, pre-specified exploratory analyses of AD patients, MMSE 14 – 4, vs. placebo, without chronic Namenda, Farlow et al., J. Alz. Dis., 2019). In a second pilot trial, Bryostatin caused significant SIB improvement (+4.12 over baseline) in the pre-specified Moderate Stratum (MMSE 10 – 14) of advanced AD patients without Namenda ($p < .005$, 2-tailed). In both trials, trend analyses demonstrated increased drug benefit with increasing dosing number. In a pooled trend analysis of Studies #202, 203, Bryostatin caused highly significant benefit ($p<.001$) and Placebo was NS.

Conclusion: While issues such as baseline imbalance (Study #203) and Namenda blockade of Bryostatin efficacy (Study #202) prevented reaching primary endpoints, these pre-specified exploratory analyses (see above) revealed clear evidence of Bryostatin therapeutic efficacy, now being tested in an NIH-sponsored, 6-month trial, incorporating lessons learned from these pilot studies. This potential efficacy involved significant improvement over baseline, not only reduction in the rate of cognitive decline.