A Phase I, Randomized, Double-Blind, Placebo-Controlled, Multiple Ascending Dose Study of AT-001 Yeast Selenium for the Prevention of Alzheimer's

Ronan Murphy, MD[1] • Erin Abner, PhD[2] • Richard Kryscio, PhD[3] • Mark Lovell, PhD[4] • Ronan Power, PhD[5] • Gregory Jicha, MD, PhD[1]

[1]Neurology, University of Kentucky • [2]Epidemiology, University of Kentucky • [3]Biostatistics, University of Kentucky • [4]Chemistry, University of Kentucky • [5]Alltech Inc.

Background: AT-001 is a yeast-based selenium supplement that has demonstrated disease modifying properties in animal models of Alzheimer's (AD). While selenium-based compounds have been widely explored for potential disease modifying properties in cancer, human studies of such compounds for the prevention or treatment of AD are lacking.

Methods: We conducted a randomized (1:3), double-blind, placebo-controlled, multiple ascending dose study of AT-001 yeast selenium for the prevention of Alzheimer's disease in 24 elderly subjects with normal cognition. Dose arms included 0,100, 200, and 400 mg AT-001 (n=8 per arm), each over a 12 week treatment period. Safety and tolerability at each dose were the primary outcomes to merit escalation. Secondary outcomes included pharmacokinetics and CSF penetration; exploratory outcomes included measures of oxidative stress, inflammation, and CSF Ab.

Results: Dose escalation was successful. At all doses tested the treatment was well tolerated with no observed treatment-related SAEs or dose limiting toxicities. Serum pharmacokinetic profiles demonstrated a dose dependent increase in AT-001 levels over the 12 week treatment period without saturation effects. CSF pharmacokinetics showed minimal change in selenium levels with 100mg dosing, a 60% increase with 200 mg dosing, and a 300% increase with 400 mg dosing. No significant changes in isoprostane or other oxidative stress biomarkers were seen at any dose. Prostaglandin E2 levels were significantly reduced by treatment in the high dose (400 mg) group only when compared to placebo ($p<0.05$). AD-like decreases in CSF Ab levels seen in the placebo subjects over the study period were attenuated by treatment, although this did not reach statistical significance ($p<0.1$).

Conclusions: AT-001 is safe and well tolerated in humans. Its pharmacokinetic profile demonstrates CSF penetrance sufficient to exert a meaningful biologic effect on CNS function. Its pharmacodynamic effects include reductions in systemic inflammation and a trend towards normalization of CSF biomarkers of AD in the elderly subjects studied. AT-001 is a readily available, low-cost supplement with the potential to prevent AD. Further clinical evaluation of AT- 001 in larger human studies of aged subjects at risk for AD is needed to confirm and expand on the present findings. We further present on the experimental design and implementation of a Phase IIa ongoing study at the University of Kentucky.