were enrolled to be followed for 18 months. The last participant is scheduled to complete the trial in March 2005. Half of the participants were randomized (double-blind) to their best tolerated dose of FGZ (15, 30, or 45mg/day) and the others to placebo. Adverse events and safety monitoring are the primary outcomes. Standard measures of symptomatic efficacy (MMSE, NPI, ADL scales, ADAS-cog and CGIC) are obtained every 3 months in an attempt to discern effect size for planning subsequent trials. Participants are permitted to continue on stable cholinesterase inhibitor therapy and those with moderate and severe AD are permitted to take memantine. **Results:** Expected adverse events such as edema, and laboratory changes including asymptomatic hypoglycemia and elevated liver enzymes have been observed at a low proportion of subjects. **Conclusions:** Epidemiologic and in vitro studies clearly support a role for inflammatory mediation of AD progression. The failure of prednisone, hydroxychloroquine, nonspecific COX inhibitors, and COX-2 inhibitors to alter the rate of decline in AD suggests that nonspecific anti-inflammatory approaches are insufficient to meaningfully slow progression of AD’s underlying pathophysiology. Targeting microglial gene transcription, and its role in inflammatory mediation with the PPAR-gamma agonist pioglitazone, offers a theoretically and experimentally justified alternative, and warrants continued investigation.

**PI-398**  
**THE EFFECTS OF SUBCLINICAL HYPOTHYROIDISM ON WORKING MEMORY: AN FMRI STUDY**  
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**Background:** Early study showed that patients with thyroid function disorders have higher risk to get dementia. The effects of subclinical hypothyroidism (SCH) on adult cognitive functions are poorly understood. **Objective(s):** To evaluate the working memory impairment of SCH patients and the effect of L-Thyroxine treatment on such deficiency. **Methods:** Using functional magnetic resonance imaging (fMRI), we evaluated the brain activation of SCH before and after L-Thyroxine treatment in the n-back (n = 0, 1, 2) working memory tasks. 6 middle-aged female SCH and 6 healthy age-matched female euthyroid controls attended the experiment. **Results:** The average brain activation of SCH patients before L-Thyroxine treatment was significantly higher than that after L-Thyroxine treatment. This difference could not be attributed to the influence of L-Thyroxine on the BOLD signal. In addition, the brain activation patterns of SCH patients before L-Thyroxine treatment were less sensitive to the load of the n-back task than those after the treatment. After the treatment, the brain activation patterns in SCH patients were similar to the patterns of the euthyroid control subjects. **Conclusions:** The cognitive disturbance may be one of the early symptoms in SCH. In our experience, as soon as the SCH patients showed the cognitive impairment, the T4 treatment should be applied.

**PI-399**  
**RESPONDERS TO MEMANTINE TREATMENT IN MODERATE TO SEVERE ALZHEIMER’S DISEASE**  
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**Background:** Memantine, a low-moderate-affinity, NMDA receptor antagonist, is a novel Alzheimer’s disease (AD) therapy approved in the U.S. in October 2003 for the treatment of moderate to severe AD and also available in the EU since 2002. A 28 week, double-blind, placebo-controlled U.S. trial tested the efficacy of memantine (20 mg/day) on global, functional, and cognitive domains in 252 moderate to severe AD patients. Responder rates are indicators of the clinical relevance of treatment effects in clinical trials. **Objective:** To evaluate responder rates from a recent U.S., double-blind, placebo-controlled, sequential, escalating, single-dose study in 24 healthy subjects to assess the safety, tolerability, PK, and PD of SRA-333. **Methods:** Three dose levels (2, 5, and 10 mg) were assessed in cohorts of 8 subjects (6 active and 2 placebo) each. Assessments consisted of safety evaluation (vital signs, ECG, and laboratory tests) up to 48 hours after dose administration, determination of SRA-333 PK profile, and cognitive assessment using the Cognitive Drug Research battery (Reading, UK) exploring attention, sensori-motor tasks, and working and episodic memory. **Results:** SRA-333 was well tolerated up to a dose of 10 mg where dose-limiting mild to moderate CNS adverse events occurred (light-headedness, euphoria, sensory disturbances, and dizziness). No clinically significant sustained individual drug-related changes were recorded in vital signs, ECGs, or routine laboratory test results. No clinically relevant impairment in cognitive functions was observed. SRA-333 was rapidly absorbed (tmax = 2–10 h) and eliminated (half-life = 2–8 h). Plasma concentrations increased in a linearly dose-proportional manner with increasing doses. **Conclusions:** In summary, SRA-333 was safe and well-tolerated up to a dose of 10 mg. Its PK profile allowed a twice-daily dose regimen.