

Experimental Agent Improves Memory in MCI, Supports Targeting of Tau Pathology

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July 30, 2008 (Chicago, Illinois) — An experimental amino acid peptide that targets neurofibrillary tangles appears to improve memory in patients with amnesic mild cognitive impairment.

Results of a 12-week, phase 2a, double-blind, placebo-controlled study to evaluate the safety and tolerability of AL-108 (Allon Therapeutics Inc.), presented here at ICAD 2008: Alzheimer's Association International Conference on Alzheimer's Disease, showed that the drug had a positive effect on memory that was durable at 16 weeks in subjects randomized to the high-dose group (15 mg twice daily).

However, the trial missed its primary efficacy end point — a composite of cognitive memory scores from the memory components of 4 cognitive tests — but did show a trend toward efficacy at weeks 8 and 16.

Nevertheless, study investigator Donald Schmechel, MD, from Duke University, in Durham, North Carolina, said researchers were excited to find that there was a statistically significant effect in 2 of the secondary outcome measures.

"AL-108 has a clear and meaningful effect on working memory. These results showed significant improvement in cognition after 4 weeks of treatment and the medication was safe and well tolerated," Dr. Schmechel told reporters.

Validation of the Tau Hypothesis

According to Dr. Schmechel, this study is the first to validate, in a clinical setting, the targeting of the tau pathway in the treatment of Alzheimer's disease.

The study looked at 144 subjects, aged 55 to 85 years, from 16 clinical centers in the United States with self-reported memory complaints, confirmed by spouse or companion, Mini Mental State Exam scores of 24 or more, and Wechsler Memory Scale III age-adjusted Logical Memory II scores of 5 or less.

Participants were randomized to receive placebo, low-dose AL-108 (5 mg daily), or high-dose AL-108 (15 mg twice daily), delivered intranasally. Cognitive testing was conducted 4 weeks before drug administration, at baseline, and then at 4, 8, 12, and 16 weeks.

The composite primary end point included components from the digit span, delayed-match-to-sample (DMTS), spatial working memory, and paired-associates learning tests.

The secondary end points consisted of the individual scores from each of these 4 tests, plus scores from the One Touch Stockings of Cambridge and the Spielberger State & Trait Anxiety tests.

Positive Effect on Memory Executive Function

The investigators found that subjects in the high-dose group had statistically significant improvements in DMTS scores (a 34.2% change from baseline at 4 weeks and a 62.4% improvement at 16 weeks). This test measures attention and visual working memory.

In addition, there was a significant improvement on the digit span forward test (which measures verbal recall, executive function, and working memory) at week 8 (an 11.2% change from baseline). This result remained significant at week 16 (an 11.7% change from baseline).

There was no difference in outcome between the placebo group the low-dose group. Furthermore, there was no difference in adverse event rates between placebo- and AL-108-treated subjects.

Dr. Schmechel said the study's findings support a strategy of targeting tangle pathology and provide the impetus for a phase 2 study targeting tau pathology in mild to moderate Alzheimer's disease.

Not Powered to Show Efficacy

Asked by *Medscape Neurology & Neurosurgery* to comment on the study, Ronald Petersen, MD, PhD, director of the Alzheimer's Disease Research Center at the Mayo Clinic, in Rochester, Minnesota, and spokesperson for the Alzheimer's Association, said that the study results should be kept in perspective.

"Phase 2 trials are not powered to show efficacy. These findings are encouraging and signal that there may be merit in pursuing further research," he told *Medscape Neurology & Neurosurgery*.

However, he added, the fact that tau therapies are now being tested in the clinical setting is noteworthy. "This is 1 of 2 phase 2 trials being presented at this meeting, which has never happened before. The [investigators of these studies] are sufficiently excited about them that they are going to move forward with further research, but does that mean that these drugs are efficacious? We'll have to see," he said.

Dr. Schmechel has disclosed no relevant financial relationships.

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