**The Effects of Donepezil on Alzheimer’s Disease Progression Monitored by MRI**

**STUDY OVERVIEW**

**INTRODUCTION**

- Donepezil and other cholinesterase inhibitors have been shown to have a significant improvement in memory with slight or no improvement in activities of daily living.
- In using 612 patients with AD, progression to dementia remained similar within 6 years of diagnosis.
- Donepezil has been shown to slow disease progression by a period of 3.5 years, and is signifi-cantly improved Modified Alzheimer Disease Assessment Scale-cognitive subscale (ADS-CS).
- Donepezil has been shown to improve quality of life in AD patients with mild to moderate dementia.

**OBJECTIVES**

- To demonstrate the effects of donepezil on the rate of hippocampal, entorhinal cortex, whole brain, and cerebrospinal fluid changes over time.
- To assess the correlation of brain volumes with clinical assessment measures.

**CONCLUSIONS**

- Donepezil treatment was associated with small but significant improvements in mADAS-cog scores, but not CDR-SB scores.
- Donepezil treatment was associated with improvement in subjective patient measures.
- There were no statistically significant effects of donepezil on hippocampal, entorhinal, or whole brain atrophy volumes, change in the brain volumes, or percent change in the brain volumes per year.
- Whole but significant correlations were observed between declining cognition and smaller hippocampal, entorhinal, and whole brain atrophy volumes.
- These preliminary brain volumetric analyses showed a high degree of variability, which likely affected the results; further analyses are ongoing to explain the variance.

**RESULTS**

- Preliminary results are presented. Final results will be presented at a future meeting.
- A total of 612 patients were randomized to donepezil and 111 to placebo; 284 on donepezil and 111 on placebo were included in the intent-to-treat (ITT) population.
- 111 patients included in the ITT population; 57 patients elected to discontinue donepezil between visits 1 and 2.
- The treatment groups had comparable data in the treatment groups of the overall study, and the treated and untreated patients in the MRI subpopulation had similar amounts of atrophy (Table 1).

**Efficacy Outcomes**

- Donepezil improved relational scoring but had no effect on CDR-SB scores in the ITT population of the parent study (Table 2).
- Donepezil had no statistically significant effect on secondary efficacy measures, except for an improvement in MMSE and Trail Making test time.
- Correlations between brain volumes and clinical assessments at both baseline and study end point and between the percent rate of change in brain volumes per year and the change in clinical assessments were performed on the combined donepezil group (Table 3).
- There were few, if any, statistically significant correlations of all measured brain volumes with mADAS-cog scores at baseline and study end point.
- There were similar correlations for the 9 measured brain volumes with CDR-SB scores at study end point, but there was no correlation at baseline.
- In general, these were not consistent with the percent rate of change in brain volumes per year with changes in clinical assessment scores (CDR-SB scores).
- Treatment differences in brain volumes and correlations with clinical assessments were generally not observed in the placebo group, and the exceptions were not consistent.
- A significant treatment difference between donepezil and placebo in relational adjusted SC DRS volume (p < .001).
- A significant correlation of brain volumes and CDR-SB at end point in patients with a significant change in cognition.
- A significant correlation of hippocampal volumes and CDR-SB at end point in patients with a significant change in cognition.
- A significant correlation of brain volumes and CDR-SB at end point in patients with a significant change in cognition.
- A significant correlation of hippocampal volumes and CDR-SB at end point in patients with a significant change in cognition.

**Efficacy Outcomes**

- There were significant correlations for 6 of the 9 measured brain volumes with CDR-SB scores at study end point, but there was no correlation at baseline.
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**CONCLUSIONS**

- Donepezil treatment was associated with improvement in subjective patient measures.
- There were no statistically significant effects of donepezil on hippocampal, entorhinal, or whole brain atrophy volumes, change in the brain volumes, or percent change in the brain volumes per year.
- Whole but significant correlations were observed between declining cognition and smaller hippocampal, entorhinal, and whole brain atrophy volumes.
- These preliminary brain volumetric analyses showed a high degree of variability, which likely affected the results; further analyses are ongoing to explain the variance.

**REFERENCES**

1. Fox NC, et al. 
5. T. Claus, PhD, of PAREXEL and was funded by Eisai Inc. and Pfizer Inc.

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**METHODS**

Study Design

- A 12-month, randomized, double-blind, placebo-controlled, double-dummy trial conducted in 13 centers in the United States with both placebo arms progressed over a period of 2 years.

Study Entry Criteria

- Diagnosis of probable or possible AD according to NINCDS-ADRDA criteria. Moderate to severe AD (Mini-Mental State Examination [MMSE] score of 10 to 20).

Efficacy Measurements

- Clinical assessment measures were the mADAS-cog and the CDR-Sum of boxes (CDR-SB).
- Efficacy measures were assessed using procedures that assured the quality and standardization of the MRI acquisition and the volume assessments.

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