

## 2. SYNOPSIS

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Only)

<b>Name of Sponsor Company:</b> Eisai Limited	Individual Study Table Referring to Part of the Dossier  Volume:  Page:	
<b>Name of Finished Product:</b> Donepezil (Aricept®)		
<b>Name of Active Ingredient:</b> Donepezil hydrochloride		

**Title of Study:** A 24-week, multicentre, randomised, double-blind, placebo-controlled study of the efficacy, tolerability and safety of donepezil (Aricept®) in Parkinson's Disease (PD) patients with dementia

**Investigators:** Professor Roy Jones (UK), Professor Bruno Dubois (France), Professor Thomas Muller (Germany, Professor Marco Onofri (Italy, Portugal and Belgium), Dr Eduardo Tolosa (Spain), Professor Bryan Kies (South Africa), Dr Victor Fung (Australia and New Zealand), Dr Alan Goodridge (Canada), Professor Miroslav Mikhailovich Odinak (Russia)

**Study centre(s):** UK (15), France (12), Germany (13), Italy, Portugal and Belgium (33), Spain (11), South Africa (7), Australia and New Zealand (14), Canada (9), Russia (9)

**Publication (reference)** None

<b>Studied Period:</b> From: 16 August 2002 To: 27 June 2005	<b>Clinical Phase:</b> Phase III
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### **Objective(s):**

#### Primary Objectives:

- To assess the effects of donepezil on cognitive and global clinical function in PD patients with dementia, assessed by the Alzheimer's Disease Assessment Scale-cognitive subscale (ADAS-cog) and the Clinician's Interview Based Impression of Change with caregiver/study partner input (CIBIC-plus) scales respectively.
- To assess the tolerability and safety, including motor function (using the Unified Parkinson's Disease Rating Scale (UPDRS) motor subscale), of donepezil in PD patients with dementia.

#### Secondary Objective:

- To assess the effects of donepezil on activities of daily living (ADL) and behaviour in PD patients with dementia.

**Methodology:** A multicentre, randomised, double-blind, balanced three-arm, parallel group study of donepezil versus placebo

**Number of Patients:** Planned: 468 (156/treatment arm)  
Analyzed: 550

<b>Demographics:</b>		<b>Groups</b>		
		5 mg Donepezil (N=195)	10 mg Donepezil (N=182)	Placebo (N=173)
Male/Female		127/68	136/46	113/60
Mean Age (yrs)		72.0	70.8	72.9

**Diagnosis and Criteria for Inclusion:** Patients aged  $\geq 40$  years with an established diagnosis of Parkinson's disease (PD) and dementia with onset of dementia documented to have occurred at least 1 year after the diagnosis of PD.

**Test Drug (Batch/Lot No):** Donepezil 5 mg batch numbers 1047013 and 3096708

**Dosage:** Donepezil 5 mg or Donepezil 10 mg.

**Route:** Oral.

**Duration of Treatment:** 24 weeks. For the first 4 weeks, all patients randomised to the active treatment received 5 mg donepezil as a single dose per day. After the first 4 weeks, patients in the donepezil 5 mg treatment group continued to receive the 2 tablet single dose (5 mg donepezil tablet and a matching placebo tablet) and patients in the donepezil 10 mg treatment group received 10 mg donepezil as a 2 tablet single dose (2x5 mg donepezil tablets).

**Reference Therapy (Batch/Lot No):** Placebo batch numbers 1057607 and 3108303

**Dosage:** Placebo.

**Route:** Oral.

**Criteria for Evaluation:**

Primary Efficacy Variables

- Change from baseline (Visit 2) to Week 24 in the total Alzheimer's disease assessment scale-cognitive (ADAS-cog) score.
- Overall impression of change at Week 24 from the Clinician's Interview Based Impression of Change with caregiver/study partner input (CIBIC-Plus).

Secondary Efficacy Variables

- Change from baseline to Week 12 in the total ADAS-cog score.
- ADAS-cog sub components at Weeks 12 and 24.
- Change from baseline to Weeks 12 and 24 in the total number of correctly answered items in the Brief Test of Attention (BTA).
- Change from baseline to Weeks 12 and 24 in the row average total number of correct responses in Delis-Kaplan Executive Function System (D-KEFS) verbal fluency tests.
- Change from baseline to Weeks 12 and 24 in the total Mini-Mental State Examination (MMSE) score.
- CIBIC-Plus overall impression of change score at Weeks 4 and 12.
- The sub domain scores from the CIBIC-Plus at Weeks 4, 12 and 24 (General Domain, Mental / Cognitive, Behaviour and Activities of Daily Living).
- Change from baseline to Weeks 12 and 24 in the overall derived Disability Assessment in Dementia (DAD) score and derived domain sub scores.

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- Change from baseline to Weeks 12 and 24 in the total score from the Schwab and England scale.
  - Change from baseline to Weeks 12 and 24 in the total Neuropsychiatric Inventory (NPI) across both the neuropsychiatric and neurovegetative scores.

#### Safety Variables

- Change from baseline to Weeks 12, 24 and 28 in the total Unified Parkinson's Disease Rating Scale (UPDRS) score for UPDRS Parts I and II
- Change from baseline to Weeks 4, 8, 12, 24 and 28 in the total UPDRS score for UPDRS Part III
- Change from baseline to Weeks 4, 12 and 24 in the total UPDRS score for UPDRS Part IV
- Clinical Global Impression of Change – Parkinson's Disease (CGIC–PD) score at Weeks 4, 8, 12, 24 and 28.
- Change from baseline to Weeks 12 and 24 in the Montgomery Åsberg Depression Rating Scale (MADRS) score.
- Change from baseline to Weeks 4, 8, 12, 24 and 28 in vital signs.
- Neurological examination at screening, baseline, Weeks 4, 8, 12 and 24.
- Physical examination at screening, baseline, Weeks 4, 8, 12 and 24.
- Overall compliance.
- Electrocardiogram (ECG).
- Changes from screening to Weeks 24 and 28 in clinical laboratory parameters.
- Concomitant medications.
- Exposure.

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**Statistical Methods:** All statistical tests were 2-tailed and performed at the 5% significance level unless otherwise stated. Interactions were tested at the 10% level unless otherwise stated.

The change from baseline to Week 24 in the total ADAS-Cog score was summarised by treatment group, together with the actual value at baseline and actual value at Week 24. Between-treatment comparisons were performed on the change from baseline in the total ADAS-Cog score using an analysis of covariance (ANCOVA) model including terms for pooled country and baseline score as a covariate. The Bonferroni-Hochberg adjustment was used in order to maintain the overall experiment-wise error rate at 5% for the primary comparisons. For the secondary comparison of donepezil 5 mg and 10 mg combined vs placebo, no multiplicity adjustment was made, and no adjustment was made for the donepezil 5 mg vs donepezil 10 mg comparison. Least squares means were used for all final inferential purposes and not the row means. The simultaneous 95% confidence interval for the difference between each donepezil vs placebo comparison was derived by using the critical values from the Bonferroni-Holme procedure as an approximation. The simultaneous 95% confidence intervals were derived for estimation purposes only. Inference was based on the adjusted p-values. In addition, the 95% confidence interval for the combined donepezil vs placebo and donepezil 5 mg vs donepezil 10 mg was derived without adjustment to the

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alpha level, to provide an estimate of where the true treatment effect lies.

The overall impression of change at Week 24 of the CIBIC-Plus was summarized by treatment group. CIBIC-Plus at week 24 was analyzed using the Cochran-Mantel-Haenszel (CMH) procedure with country with MODRIDITS as the scoring option in the computation of raw mean scores. An ANCOVA model including terms for country and baseline (CIBIS) score was also performed. The Bonferroni-Hochberg adjustment was used in order to maintain the overall experiment-wise error rate at 5% for the primary comparisons. For the secondary comparison of donepezil 5 mg and 10 mg combined vs placebo, no multiplicity adjustment was made, and no adjustment was made for the 5 mg vs 10 mg comparison.

Statistical analyses for secondary efficacy parameters were performed similarly to those performed for the primary endpoints. Treatment contrasts between donepezil vs placebo comparisons were derived and 95% confidence intervals for contrasts were also provided. No adjustments were made for multiplicity. Statistical analysis of Week 12 for any given secondary endpoint by way of hypothesis tests was only carried out if the parameter was statistically significant at Week 24. However, summary statistics were provided over all time points.

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## **SUMMARY – CONCLUSIONS:**

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### **RESULTS:**

**Efficacy:** There was evidence for dose-dependent improvement in cognition assessed by the co-primary endpoint, ADAS-cog. Week 24, ITT (LOCF), mean (SD) changes from baseline were: placebo -0.3 (6.491), donepezil 5 mg -2.45 (5.278), and donepezil 10 mg -3.72 (7.054).

All the analyses for the primary endpoint of ADAS-cog showed similar results, with the exception of those observed for the unweighted planned analysis as specified in the SAP with interaction term included in the model. The results of planned analysis showed a strong treatment-by-country interaction ( $p < 0.001$ ) and no statistically significant treatment effect ( $p > 0.05$ ). However, when omitting the interaction term, a highly statistically significant treatment effect was observed ( $p < 0.001$ ). A similar treatment effect was observed for all other ANCOVA analyses for ADAS-cog presented ( $p < 0.001$ ). These analyses showed a clear difference between donepezil 10 mg and placebo ( $p < 0.001$ ) and donepezil 5 mg and placebo ( $p < 0.05$ ).

A treatment effect was observed in the comparison of donepezil 10 mg vs placebo for the CIBIC-plus primary analysis endpoint ( $p = 0.040$ ). However, when adjusting for multiplicity assessing, the results would be considered non-significant at the 5% level for CIBIC-plus (adjusted  $p = 0.081$ ). The results of the ANCOVA primary analyses model showed a significant treatment effect for donepezil 10 mg ( $p = 0.014$ , adjusted  $p = 0.029$ ). No significant difference was observed in the comparison of donepezil 5 mg vs placebo ( $p \geq 0.1$ ). Other analyses for CIBIC-plus showed similar results.

Clear improvements were seen for most ADAS-cog and CIBIC-Plus components between baseline and Week 24 for the donepezil groups as compared to very little change, or slight

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worsening in the placebo group.

In all cases, there was a statistically significant difference between donepezil and placebo in the analysis of change from baseline in MMSE score ( $p < 0.001$ ). Similar results were seen for more specific cognitive tests particularly relevant for this type of dementia: highly statistically significant improvements were seen in both donepezil groups for D-KEFS verbal fluency ( $p < 0.01$ ) as compared to a general worsening in the placebo group. Similarly, the BTA showed statistical significant improvements in both donepezil groups as compared to a worsening in the placebo group ( $p < 0.01$ ).

In general, mean changes from baseline for DAD scores were small. Mean (SD) overall score baseline values were 67.17 (23.99), 63.34 (23.81), and 66.12 (22.97) in the donepezil 5 mg, donepezil 10 mg, and placebo groups, respectively (ITT-LOCF). There was no statistically significant change from baseline or difference between the treatment groups. The components of initiation, planning and organization, and effective performance for all ADL showed similar results.

There was a slight reduction from baseline in the Schwab and England scale in all treatment groups. There were no statistically significant differences between the treatment groups.

Mean (SD) baseline total NPI scores were 13.53 (12.82), 14.51 (11.44), and 12.15 (10.42) in the donepezil 5 mg, donepezil 10 mg, and placebo groups, respectively (ITT-LOCF), showing a low baseline level of morbidity. There was a slight reduction (improvement) from baseline in total NPI score in the donepezil groups. There were no statistically significant differences between the treatment groups.

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**Safety:** The results presented in the current report are consistent with the known safety profile of donepezil. Donepezil was well tolerated. There was no evidence of unexpected adverse events related to treatment with donepezil. The safety profile seen in this study is consistent with that expected in an elderly PD population.

As expected, there was a higher incidence of nausea, vomiting, and diarrhoea in the donepezil groups as compared to placebo. There was no evidence to suggest any other relevant differences between the treatment groups in the AE profiles. Four patients in the donepezil 5 mg group, one patient in the donepezil 10 mg group and five patients in the placebo group died during the study. Of these, one patient in each donepezil group died due to an event determined by the investigator to be possibly related to study medication, although the sponsor considered the deaths likely to be due to other factors. There were no notable differences between the treatment groups with regard to the frequency or nature of SAEs.

Laboratory and physical examination parameters remained largely unchanged throughout the course of the study.

A slightly higher percentage of patients reported worsening of Parkinsonian symptoms (10.8% and 10.4% in the donepezil 5 mg and 10 mg, respectively, vs 6.9% in the placebo group). In addition, tremor as an AE was reported more commonly in both donepezil groups

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(7.2% patients at 5 mg dose and 7.1% at 10 mg dose) than in the placebo group (2.9%). A slightly higher proportion of patients had moderate or marked worsening of Parkinsonian symptoms at Week 24 (including early terminators) as assessed by the CGIC-PD scale on donepezil compared to placebo (10.4% patients on donepezil 10 mg vs 7.1% on donepezil 5 mg vs 5.3% on placebo). However, there was no statistically significant difference between treatment groups in change from baseline in the analysis of UPDRS Part III at Weeks 12 or 24. The treatment groups were shown to be equivalent at Weeks 12 and 24 for UPDRS Part III. No statistically significant differences were found between the treatment groups in the MADRS scores, showing no effect on depressive symptoms.

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**CONCLUSIONS:** Statistically significant and clinically meaningful improvements were seen in ADAS-cog, with a clear difference between donepezil 10 mg and placebo and donepezil 5 mg and placebo. Slightly greater improvements were seen in the 10 mg donepezil

treatment group when compared to the 5 mg treatment group: at Week 24, LOCF, mean (SD) changes from baseline were donepezil 5 mg -2.45 (5.278), and donepezil 10 mg -3.72 (7.054).

Improvement in cognition was also observed on secondary measures including the MMSE and tests of executive function and attention, which are especially relevant in this patient population.

There was evidence for a treatment effect observed in the comparison of donepezil 10 mg vs placebo for the CIBIC-plus, confirming that clinically relevant changes in global function may be observed under donepezil treatment. This difference was not significant for the 5 mg dose group.

No significant effect on ADL assessments were observed in the current study, nor were consistent effects on behaviour, although the incidence of behavioural disturbances in the population overall was low.

Overall, the study provides evidence that donepezil improves cognition and global function in patients with PD related dementia. Although there is evidence for efficacy at both the 5 mg and 10 mg dose levels, efficacy is greater at the 10 mg dose. Tolerability is generally good and similar to that in AD, although there is a slight increase in the frequency of reports of worsening of Parkinsonian symptoms and tremor on donepezil, particularly at the 10 mg dose.

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**Date of the Report:** 16 February 2010

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