

## PFIZER INC.

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**PROPRIETARY DRUG NAME/INN:** Aricept®/Donepezil

**THERAPEUTIC AREA AND FDA APPROVED INDICATIONS:** See USPI

**PROTOCOL NO.:** A2501017

**PROTOCOL TITLE:** A Six-Month, Multicenter, Double-Blind, Parallel, Placebo-Controlled Study of the Effect on Global/Behavioural/ADL Functions and Tolerability of Aricept® in Patients with Severe Alzheimer's Disease Living in an Assisted Care Facility

**Study Center(s):** 50 centers in Sweden

**Study Initiation and Completion Dates:** 10 October 2002 to 29 October 2004

**Phase of Development:** Phase 3

### **Study Objective(s):**

*Primary:* To compare the change from baseline to the 6-month visit, between donepezil-treated and placebo-treated patients, in the Severe Impairment Battery (SIB scale) and the Modified Alzheimer's Disease Cooperative Study Activities of Daily Living Inventory for Severe Alzheimer's Disease (ADCS ADL severe scale).

*Secondary:* To evaluate the efficacy during the 6-month trial of donepezil versus placebo on measures including the Neuropsychiatric Inventory (NPI), the Mini Mental State Examination (MMSE), and the Clinical Global Impression of Improvement (CGI-I). Other secondary objectives were to evaluate safety and tolerability.

### **METHODS**

#### **Study Design:**

This was a 6-month multicenter, randomized, double-blind, placebo-controlled, parallel-group study in patients with severe Alzheimer's Disease (AD) living in assisted care facilities (skilled nursing homes). Eligible subjects were randomized 1:1 (donepezil:placebo) to a starting dose of donepezil 5 mg/day or matching placebo respectively. After 1 month on study medication, the patient's dose was to be increased to 10 mg daily according to the clinician's judgment of tolerability. At any time during the study the investigator had the option to reduce the dose from 10 mg to 5 mg daily, based on tolerability.

Vital signs and safety were assessed at baseline (Visit 1) and at 1 month (Visit 2), 3 months (Visit 3), and 6 months (Visit 4) after initiating study medication. Efficacy parameters were the Severe Impairment Battery (SIB), Modified Alzheimer's Disease Cooperative Study Activities of Daily Living Inventory for Severe Alzheimer's Disease (ADCS-ADL-severe),

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Neuropsychiatric Inventory (NPI), Clinical Global Impression of Improvement (CGI-I), and the Mini Mental State Examination (MMSE). Efficacy was assessed at baseline, Visit 3 (month 3), and Visit 4 (month 6) for all parameters, except MMSE (at inclusion and visit 4) and CGI-I (Visits 3 and 4). Assessments were to be scheduled at the same time of day at each visit whenever possible. A subject was considered to have completed the study after receiving 6 months of double-blind treatment and completing the Visit 4 (month 6) assessments.

### **Number of Patients (planned and analyzed):**

Planned enrollment was 280 subjects (140 donepezil, 140 placebo); 248 subjects received treatment and were analyzed (128 donepezil, 120 placebo).

### **Diagnosis and Main Criteria for Inclusion:**

Eligible subjects were ambulatory or ambulatory-aided males or females over 50 years of age with probable or possible Alzheimer's disease consistent with Diagnostic and Statistical Manual of Mental Disorders, Fourth edition (DSM-IV) and National Institute of Neurological and Communicative Disorders and Stroke – Alzheimer's Disease and Related Disorders Association (NINCDS-ADRDA) criteria. Subjects were living in assisted care facilities (skilled nursing homes) and had a level of dependence supported by scoring within defined limits on the MMSE (1-10) and Functional Assessment Staging Scale (FAST) (5-7c), designed to enroll only severe AD patients. Subjects had a computerized tomography (CT) or magnetic resonance imaging (MRI) consistent with a diagnosis of Alzheimer's disease without any other clinically significant change in clinical status suggestive of stroke or other possible neurological disease with onset between the time of the last CT/MRI and the inclusion evaluation.

### **Study Treatment:**

Subjects received one 5-mg tablet of study medication daily for 30 days, and then one 10-mg tablet daily thereafter. The first dose was administered at the randomization visit; subsequent doses were administered each evening, just prior to bedtime, through to the completion of the 6-month treatment period. Subjects were instructed to take study medication with a full glass of water. During the study, a modification to the time of dosing of study medication was allowed; subjects who could not tolerate administration of study medication in the evening were permitted to take the study medication in the morning. At any time during the study the investigator had the option to reduce the dose from 10 mg to 5 mg daily, based on tolerability.

### **Efficacy Evaluations:**

*Primary:* The effects of donepezil on cognition and patient function was based on differences between the active and placebo treatment groups for two parameters: change from baseline to Visit 4 (month 6) in the SIB scale (total score) and change from baseline to Visit 4 (month 6) in the modified ADCS-ADL-severe scale (total score).

*Secondary:* The effects of donepezil on cognition and patient function were further evaluated by comparing the effects of active and placebo treatment on the following secondary efficacy variables: change from baseline to Visit 3 (month 3) in the SIB scale (total score), the modified

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ADCS-ADL-severe scale (total score), and the NPI (total score); change from inclusion in study to Visit 4 (month 6) in the MMSE (total score); change from baseline to Visit 4 (month 6) in the NPI (total score); and CGI-I score at Visit 3 (month 3) and Visit 4 (month 6).

### **Safety Evaluations:**

Vital signs were assessed at all visits, and electrocardiograms, physical and neurological evaluations, and clinical laboratory measurements were assessed at inclusion and the final visit to identify any clinically significant changes. All observed or volunteered adverse events (AEs) were recorded throughout the study.

### **Statistical Methods:**

All statistical tests were performed at the 0.05 level of significance and were 2-tailed. Assumptions of the statistical models with regard to homogeneity of variance and normality in the continuous efficacy measures were examined. The efficacy analyses were conducted on datasets for the Intent-to-treat (ITT) and the Per Protocol (PP) populations. Both Last Observation Carried Forward (LOCF) at Visit 4 (month 6) and Observed Cases (OC) at Visits 3 and 4 (months 3 and 6, respectively) analyses were conducted in the ITT population, while only OC analyses were conducted in the PP population. The primary analysis was based on LOCF analyses in the ITT population.

The efficacy variables SIB, ADCS-ADL-severe, NPI, and MMSE were analyzed using a general linear model (GLM). Statistical analyses of continuous efficacy parameters were performed on differences in the change from baseline scores to scores at Visits 3 and 4. The GLM included treatment and baseline as a covariate. Models with baseline by treatment, center, treatment-by-center, and other statistically significant demographic variables were also explored. If the baseline-by-treatment, center and treatment-by-center effects were statistically significant at the 0.10 level, the nature of the interaction was examined. The assumptions of normality of raw (unstandardized) residuals from the ANCOVA model used for the continuous outcome measures were examined graphically. If there had been evidence that the normality assumption was seriously violated, then the data were to be analyzed using a rank ANCOVA, with treatment and baseline values as covariates. The CGI-I was analyzed using the Cochran-Mantel-Haenszel (CMH) chi-square test stratified by center using modified ridit (MODRIDIT) scores as the test statistic. Pooling over the low-enrolling centers was performed. Paired t-tests were used to compare pre-treatment with post-treatment continuous efficacy values within each treatment group. The primary analyses on the primary efficacy endpoints were the changes from baseline to Visit 4 (month 6) in the SIB total score and the ADCS-ADL-severe total score in the ITT population (LOCF).

The ITT population consisted of all subjects who were randomized and received at least one dose of donepezil or placebo and provided at least one efficacy baseline assessment and at least one corresponding post-baseline efficacy assessment. The PP population consisted of all ITT subjects who completed the full 6 months of double-blind treatment, had a medication compliance of  $\geq 80\%$  and  $\leq 120\%$ , had Visit 4 (month 6) in  $180 \pm 17$  days, completed at least 1 other clinic visit during the treatment, did not take excluded concomitant medication that would potentially

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interfere with the evaluation of efficacy, and had no other significant protocol violations (inclusion/exclusion criteria).

### **RESULTS**

#### **Subject Disposition and Demography:**

**Table 1. Summary of Patient Disposition**

	<b>Treatment Group</b>	
	<b>Donepezil</b>	<b>Placebo</b>
Subjects Screened	334	
Assigned to Study Treatment	249*	
Treated	128	120
Completed the study	95 (74.2%)	99 (82.5%)
Discontinued	33 (25.8%)	21 (17.5%)
Reason for discontinuation <sup>†</sup>		
Patient died <sup>‡</sup>	8 (6.3%)	12 (10.0%)
Related to study drug		
Adverse event	6 (4.7%)	1 (0.8%)
Not related to study drug		
Adverse event	14 (10.9%)	7 (5.8%)
Other	3 (2.3%)	0 (0.0%)
Patient defaulted <sup>  </sup>	2 (1.6%)	1 (0.8%)

\*1 of the 249 subjects was randomized but did not take study medication.

<sup>†</sup>Figures are given only for subjects who received study medication.

<sup>‡</sup>18 additional patient deaths are in the safety database. Of these 18 patients, 14 are listed as discontinued for AE (and subsequently died), and 4 are listed as completing the study (and subsequently died). One of these 18 patients died 35 days after discontinuation from the study.

<sup>||</sup>Subject withdrew consent or was lost to follow-up.

Treatment groups were similar with regard to age, sex, race, education, weight, and height. Mean age was 84.5 years in the donepezil group and 85.3 years in the placebo group, most subjects were female (78.9% donepezil, 74.2% placebo) and all but one subject (in the placebo group) were white.

Using NINCDS-ADRDA criteria at the inclusion visit, probable Alzheimer's disease was diagnosed in 83.6% of donepezil-treated subjects and in 84.2% of placebo-treated subjects; possible Alzheimer's disease was diagnosed in 16.4% of donepezil-treated subjects and 15.8% of placebo-treated subjects. Baseline values for efficacy measures (MMSE at screening, ADCS-ADL-severe, SIB, NPI) were well balanced in the donepezil and placebo groups. All subjects met the protocol-specified criteria for the FAST, and generally similar numbers of subjects in both treatment groups were present at most stages. It is notable that more than 80% of the subjects in this trial ranged from FAST stage 6c (inability to handle toileting mechanics) to 7c (ambulatory ability lost).

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### Efficacy Results:

The results of the primary efficacy analyses, the ITT-LOCF analyses on the change from baseline after 6 months of treatment in the SIB score and the ADCS-ADL-severe score were both statistically significant in favor of donepezil-treated subjects (Table 2). For the mean change from baseline to Visit 4 (month 6) in the SIB score, donepezil-treated subjects showed a mean improvement, while placebo-treated subjects showed a mean decline. This difference between groups was statistically significant for the ITT-LOCF analysis ( $p = 0.008$ ). For the mean change from baseline to Visit 4 (month 6) in the ADCS-ADL-severe score, donepezil-treated subjects showed less mean decline than placebo-treated subjects. This difference between groups was also statistically significant for the ITT-LOCF analysis ( $p=0.029$ ).

**Table 2. Primary Efficacy Analyses: SIB and ADCS-ADL-Severe Scores: Change from Baseline to Visit 4 (month 6) (LOCF)**

	Treatment Group		p-value (ANCOVA)
	Donepezil	Placebo	
SIB Total score: ITT-LOCF (N)	109	107	0.008
Baseline, mean (SD)	54.4 (23.8)	56.5 (24.1)	
Visit 4 (month 6), mean (SD)	57.9 (26.8)	54.2 (26.6)	
Mean change, LS mean (SEM)	3.4 (1.5)	-2.2 (1.5)	
ADCS-ADL-severe Total score: ITT-LOCF (N)	109	107	0.029
Baseline, mean (SD)	14.4 (9.1)	14.0 (8.5)	
Visit 4 (month 6, mean (SD)	13.0 (9.4)	11.0 (8.3)	
Mean change, LS mean (SEM)	-1.4 (0.5)	-3.0 (0.5)	

Note: Test of treatment effect based on the ANCOVA model, with baseline value as covariate.  
 ITT = intent-to-treat, LOCF = last observation carried forward, SD = standard deviation,  
 SEM = standard error mean.

The results of the secondary efficacy analyses on the SIB score and the ADCS-ADL-severe score confirmed the results of the primary efficacy analyses. For the SIB, the ITT-OC and the PP-OC analyses on the mean changes from baseline to Visit 4 (month 6) and from baseline to Visit 3 (month 3) were all statistically significant, favoring donepezil-treated subjects ( $p \leq 0.018$ ). For the ADCS-ADL-severe, the ITT-OC and the PP-OC analyses on the mean changes from baseline to Visit 4 (month 6) were statistically significant, favoring donepezil-treated subjects ( $p \leq 0.046$ ). The ITT-OC and the PP-OC analyses on the mean changes from baseline to Visit 3 (month 3) favored donepezil-treated subjects, but were not statistically significant ( $p=0.086$  and  $p=0.081$ , respectively).

Results favored donepezil treatment over placebo treatment for most secondary efficacy parameters. For the change from inclusion to Visit 4 (month 6) in MMSE score, donepezil-treated subjects showed greater mean improvement than placebo-treated subjects in the LOCF analysis on the ITT population (LS mean improvements of 1.5 and 0.1 for the donepezil and

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placebo groups, respectively). This difference was statistically significant ( $p=0.009$ ). The results of the ITT-OC analysis and the results of the PP-OC analysis were also statistically significant ( $p=0.009$  and  $p=0.017$ , respectively), confirming the results of the ITT-LOCF analysis.

For CGI-I scores at Visit 4 (LOCF analysis on the ITT population), 53.2% of donepezil-treated subjects were rated as very much improved, much improved, or minimally improved compared with 38.3% of placebo-treated subjects. In this analysis, 20.7% and 25.2% were rated as having worsened to some extent in the donepezil and placebo groups, respectively. Although the differences in the distribution of the scores in the donepezil and placebo treatment groups was not significant ( $p = 0.055$  LOCF analysis), the results of the OC analysis in the ITT population and of the OC analysis in the PP population were statistically significant, favoring donepezil, with  $p$ -values of 0.008 and 0.006, respectively. There was no significant difference between treatment groups in either the ITT-OC or PP-OC analysis of CGI-I score at Visit 3 (3 month).

For NPI, both treatment groups improved at Visit 4 (month 6), with greater improvement in the donepezil group. However, these differences were not statistically significant ( $p=0.426$ ,  $p=0.331$ , and  $0.440$  for ITT-LOCF, ITT-OC, and PP-OC, respectively). At Visit 3 (month 3), both treatment groups showed improvement in NPI, with a greater improvement in the placebo group, but the differences were not statistically significant.

### **Safety Results:**

The incidence of all-causality AEs in donepezil-treated subjects was comparable to that in placebo-treated subjects (82.0% vs 75.8%). The total numbers of AEs in donepezil-treated subjects and placebo-treated subjects were 311 and 220, respectively. The most common AEs (regardless of relationship to treatment) reported by at least 5% of subjects in either treatment group are summarized in Table 3 below. Only diarrhea and hallucinations were reported at more than twice the rate in donepezil-treated subjects compared with placebo-treated subjects (9.4% vs 2.5% and 6.3% vs 0.8%, respectively). In 3 of the 8 donepezil-treated subjects and the 1 placebo-treated subject, hallucinations were present prior to the start of the study.

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**Table 3. Adverse Events Reported by  $\geq 5\%$  of Subjects in Either Treatment Group (All Causalities)**

Adverse Event	Treatment Group	
	Donepezil N=128	Placebo N=120
Number of adverse events	311	220
Urinary tract infection	22 (17.2%)	19 (15.8%)
Accidental fall	17 (13.3%)	15 (12.5%)
Anxiety	8 (6.3%)	10 (8.3%)
Accidental injury	7 (5.5%)	6 (5.0%)
Gastroenteritis	8 (6.3%)	12 (10.0%)
Diarrhea	12 (9.4%)	3 (2.5%)
Pneumonia	12 (9.4%)	7 (5.8%)
Cystitis	8 (6.3%)	5 (4.2%)
Nausea	8 (6.3%)	5 (4.2%)
Asthenia	4 (3.1%)	7 (5.8%)
Bone fracture accidental	7 (5.5%)	4 (3.3%)
Constipation	5 (3.9%)	6 (5.0%)
Hallucinations	8 (6.3%)	1 (0.8%)

Hallucinations were considered possibly related to study medication in 3.1% of donepezil-treated subjects and 0% of placebo-treated subjects. Diarrhea was considered possibly related to study medication in 6.3% of donepezil-treated subjects and 0% of placebo-treated subjects. Most adverse events were mild or moderate in severity and were transient.

Deaths occurred during and within 30 days after the study in comparable proportions in both treatment groups: 14.1% of donepezil-treated and 15.8% of placebo-treated subjects. The proportions of subjects with SAEs (including those with an outcome of death) during the study or within the 30-day study lag period were comparable in donepezil- and placebo-treated subjects, 24.2% vs 25.8% respectively. Only 1 SAE in each treatment group was considered possibly related to study medication, and the rest were considered unrelated. For SAEs with death as an outcome, the cardiovascular and respiratory systems were most commonly involved in both donepezil- and placebo-treated subjects. Pneumonia was the most common SAE with an outcome of death in both donepezil-treated subjects and placebo-treated subjects. None of the deaths were considered related to study drug.

The rate of discontinuation for adverse events was greater in donepezil-treated subjects than in placebo-treated subjects, 15.6% vs 6.7% respectively. AEs that more commonly led to discontinuation by donepezil-treated subjects as compared to placebo-treated subjects included diarrhea (2.3% vs 0%), accidental falls (1.6% vs 0.8%), malaise (1.6 vs 0.8%), cerebrovascular accident (1.6% vs 0%), and hallucinations (1.6% vs 0%). Events that more commonly led to discontinuation by placebo-treated subjects vs donepezil-treated subjects were abdominal pain (1.7% vs 0%), anxiety (1.7% vs 0%), and pneumonia (1.7% vs 0.8%). Discontinuation for adverse events was considered most likely related to study medication in 4.7% of donepezil-treated subjects and 0.8% of placebo-treated subjects. Eight donepezil-treated subjects and 12 placebo-treated subjects discontinued due to death.

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There were no notable changes from inclusion or baseline to Visit 4 (month 6) in laboratory examination, ECG, physical examination (well-being) or vital sign findings.

### **CONCLUSION(S)**

Donepezil was found to be significantly more effective than placebo in this 6-month, multicenter, randomized, double-blind, placebo-controlled, parallel-group trial in 248 patients with severe AD who were living in assisted care facilities (skilled nursing homes). The results of the primary efficacy analyses, the ITT-LOCF analyses on the change from baseline to Visit 4 (month 6) in the SIB score and the ADCS-ADL-severe score were both statistically significant in favor of donepezil-treated subjects. These statistically significant group differences for both primary efficacy variables indicate a clinically meaningful benefit of donepezil in the treatment of severe AD. The proportions of subjects reporting AEs (all-causalities) were similar in the two treatment groups. Only diarrhea and hallucinations were reported at more than twice the rate in donepezil-treated subjects compared with placebo-treated subjects (9.4% vs 2.5% and 6.3% vs 0.8%, respectively). In conclusion, this study demonstrates that donepezil is an effective, well-tolerated, and safe treatment for patients who are in the severe stage of AD.

**Based on a report completed on:** 28 June 2005

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