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A 24-week, double-blind, placebo-controlled trial of donepezil in patients with Alzheimer's disease

S.L. Rogers, PhD; M.R. Farlow, MD; R.S. Doody, MD, PhD; R. Mohs, PhD; L.T. Friedhoff, MD, PhD; and the Donepezil Study Group*

Article abstract—The efficacy and safety of donepezil as a treatment for patients with mild to moderate Alzheimer's disease (AD) was investigated in a multicenter, double-blind study. Patients were randomly assigned to treatment with placebo (n = 162), 5 mg/d donepezil (n = 154), or 10 mg/d donepezil (n = 157) for 24 weeks followed by a 6-week, single-blind placebo washout. The primary efficacy measures were the cognitive portion of the Alzheimer's Disease Assessment Scale (ADAS-cog) and the Clinician's Interview Based Assessment of Change-Plus (CIBIC plus), with the Mini-Mental State Examination (MMSE), Clinical Dementia Rating Scale-Sum of the Boxes (CDR-SB), and patient rated Quality of Life (QoL) used as secondary measures. Cognitive function, as measured by the ADAS-cog, was significantly improved in the 5- and 10-mg/d donepezil groups as compared with the placebo group at weeks 12, 18, and 24. Clinician's global ratings on the CIBIC plus also improved in both the 5- and 10-mg/d donepezil groups relative to placebo. At the end of the 6-week placebo washout phase, ADAS-cog scores and CIBIC plus ratings were not significantly different for the three groups. Significant treatment benefits were also observed consistently in both the 5- and 10-mg/d groups on the MMSE and the CDR-SB, but there was no consistent effect on the patient-rated QoL. Cholinergic side effects (primarily diarrhea, nausea, and vomiting) were reported more often in the 10-mg/d group than either the 5-mg/d or placebo groups. Side effects were transient and generally mild in severity. These data indicate that donepezil is a well-tolerated drug that improves cognition and global function in patients with mild to moderate AD.

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Alzheimer's disease (AD) is characterized by deficits in memory and cognition that are associated with significant losses of presynaptic cholinergic function in the brain, particularly the nucleus basalis.[1-3] It has been hypothesized that cholinergic agents, either cholinesterase (ChE) inhibitors or cholinergic agonists, might improve these clinical symptoms.[4]

ChE inhibitors act by blocking acetylcholinesterase (AChE) and butylcholinesterase (BuChE), enzymes that normally hydrolyze acetylcholine. However, many ChE inhibitors lack selectivity for AChE in the CNS and consequently may have to be given at elevated doses to elicit a clinically important effect. This can result in peripheral ChE inhibition and unacceptable side effects such as dyspepsia, nausea, vomiting, and diarrhea.[5] Some ChE inhibitors such as tacrine and velnacrine also cause hepatotoxicity in many patients.[6-9] Hence, the clinical utility of some compounds in the treatment of AD has been limited by their side effects.

To date, two ChE inhibitors have been approved by the U.S. Food and Drug Administration (FDA) to treat AD: tacrine, an acridine, and donepezil hydrochloride, a piperidine. However, many other agents are used experimentally, some of which are currently undergoing systematic clinical evaluation.

*See the Appendix on page 144 for a listing of the members of the Donepezil Study Group.

From Eisai Inc. (Drs. Rogers and Friedhoff), Teaneck, NJ; the Indiana University School of Medicine (Dr. Farlow), Indianapolis, IN; Baylor College of Medicine (Dr. Doody), Houston, TX; and the Mount Sinai Medical Center (Dr. Mohs), New York, NY.

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Address correspondence and reprint requests to Dr. L. T. Friedhoff, Eisai Inc., Glenpointe Centre West, 500 Frank W. Burr Blvd., Teaneck, NJ 07666-6741.

Donepezil is an AChE inhibitor that is chemically distinct from other drugs studied for the treatment of AD. In preclinical investigations, donepezil has been shown to have greater specificity for AChE than either tacrine or physostigmine and a longer duration of action than either of these drugs.[10] The AChE:BuChE binding ratio of donepezil is the highest available in this class of agents, indicating that donepezil possesses high central versus peripheral cholinomimetic specificity[10] and, thus, a favorable efficacy to side-effect ratio and therapeutic margin. Indeed, in phase I and II studies of donepezil, no evidence of clinically significant adverse events or hepatotoxicity were observed.[11]

The present phase III study was undertaken to further evaluate the efficacy and safety of donepezil at dosage levels of 5 and 10 mg/d versus placebo in patients with mild to moderate AD.

Methods. *Patient population.* Patients eligible for this study had a diagnosis of uncomplicated AD. These men and women of any race aged 50 years or older showed no evidence of insulin-dependent diabetes mellitus or other endocrine disorders; asthma or obstructive pulmonary disease; or clinically significant uncontrolled gastrointestinal, hepatic, or cardiovascular diseases. The diagnosis of probable AD was made according to criteria outlined by the National Institute of Neurological and Communicative Disorders and Alzheimer's Disease and Related Disorders Association (NINCDS-ADRDA), with patients also fitting DSM-III-R illness categories of 290.00 or 290.10, with no clinical or laboratory evidence of a cause other than AD for their dementia.[12,13] Patients had scores on the Mini-Mental State Examination (MMSE) of 10 to 26, and a Clinical Dementia Rating (CDR) score of 1 (mild dementia) or 2 (moderate dementia) at both screening and baseline.[14,15] Patients who were known to be hypersensitive to ChE inhibitors or had been taking tacrine and/or other investigational medications within 1 month of baseline were excluded. Concomitant medications such as anticholinergics, anticonvulsants, antidepressants, and antipsychotics were not allowed during the course of this study. Drugs with CNS activity were either prohibited or partially restricted. All other medications were permitted. Patients were required to have a reliable caregiver. Written informed consent was obtained from both the patient and from their caregiver.

Study design. This was a 24-week, randomized, double-blind, placebo-controlled study, ending with a single-blind placebo washout phase of 6 weeks. Treatment group status was assigned by a computerized randomization schedule. The trial was conducted at 20 investigational sites in the United States with 473 patients being enrolled into three approximately equal groups: placebo (n = 162), donepezil 5 mg/d (n = 154), and donepezil 10 mg/d (n = 157). Patients received their treatment, a single dose, once each evening. For the maximum dosage group (10 mg/d donepezil), a blinded forced titration scheme was used in which subjects received 5 mg/d donepezil for the first week and then 10 mg/d for the remainder of the study.

Measures of clinical outcome were assessed at baseline and at 6-week intervals. Protocol-specified primary outcome measures were the cognitive portion of the Alzheimer's Disease Assessment Scale (ADAS-cog) and a Clinician's Interview-Based Impression of Change scale that included caregiver supplied information (CIBIC plus).[16,17] Protocol-specified secondary outcome measures were the MMSE, patient-rated quality of life (QoL) scale, and the Sum of the Boxes of the CDR scale (CDR-SB).[14,18,19] Donepezil concentrations in plasma were measured,[20] and an analysis quantifying inhibition of RBC AChE activity[21] was performed on blood samples collected from all patients at their baseline and at 6-, 12-, 18-, 24-, and 30-week visits. Patients who withdrew early were encouraged to return for the 24- and 30-week evaluations for retrieved dropout analyses. Safety was assessed at 6-week intervals by physical examinations, clinical laboratory tests, adverse event monitoring, and by evaluation of the general health and well-being of the patient. All patients completing the double-blind phase of this study were eligible to receive donepezil during a subsequent open-label study.

Measures of efficacy. The ADAS-cog is a sensitive and reliable neuropsychological test consisting of an 11-item scale used to assess the severity of selected areas of cognitive impairment (memory, language, orientation, reason, and praxis). Scores range from 0 to 70 with lower scores indicating lesser severity. Its use in assessing and following changes in cognitive function in patients with AD has been extensively validated.[22] On average, untreated patients with moderately severe AD show an increase (cognitive decline) of approximately 7 to 11 points per year.[23,24] However, the ADAS-cog is not uniformly sensitive over the course of the disease. Thus, scores for patients with very mild or very severe disease may increase only 0 to 5 points per year.

The CIBIC plus is not an instrument but an interview technique used by a clinician who is barred from knowledge of all psychometric test scores, laboratory values, and adverse event reports obtained as part of the protocol. The format used for this trial (CIBIC plus) was developed from the Alzheimer's Disease Cooperative Study-Clinician's Global Impression of Change (ADCS-CGIC).[17] It provides a global rating score that reflects patient function in four areas: general, cognitive, behavior, and activities of daily living. It is derived through independent and comprehensive interviews with both patient and caregiver. Clinical trials of antidementia agents have used a variety of CIBIC formats, each differing in depth and structure. The clinician first assesses disease severity at baseline. Using the results from baseline for reference, the clinician then interviews the patient and caregiver at specified times during the study to obtain an impression of change. The order of interviewees (patient and caregiver) was randomized at each visit. After the interview, a seven-point Likert-type scale is used for scoring, where 1 is marked improvement, 4 is no change, and 7 represents marked worsening.

The MMSE is a widely used brief test for evaluating the cognitive state of patients. The QoL is a patient-rated seven-item scale that evaluates the patient's feeling of well-being. The basic domains examined are relationships, eating and sleeping, and social and leisure activity. The CDR-SB sums the ratings in each of six domains ("boxes") of the CDR to provide a consensus-based global clinical measure (i.e., the Sum of the Boxes). The domains include memory, orientation, judgment and problem solving, com-

munity affairs, home and hobbies, and personal care. The ratings for each domain are agreed on by the members of the patient's assessment team, except the clinician conducting the CIBIC plus, after review and consideration of the results from all neuropsychological tests conducted during clinic visits.

Statistical assessments. Sample sizes for this study were selected based on a review of clinical studies of other ChE inhibitors[6,9] and the results of earlier phase II studies of donepezil. The analyses for efficacy in this study was performed on two patient populations: the fully evaluable and intent to treat (ITT). The fully evaluable population was defined as all patients who completed 24 weeks of double-blind treatment with at least 80% compliance of study medication at week 24 and had at least two other visits during the double-blind phase with no significant protocol violations. Intent-to-treat analysis included all subjects who were randomized to treatment, received at least one dose of the study drug, provided complete baseline data, plus a minimum of one post-baseline data point. The efficacy conclusions were based on the results at each patient's last assessment during double-blind therapy, defined as study endpoint (i.e., last observation carried forward (LOCF) as outlined by the FDA).[25] Both the 5- and 10-mg/d-donepezil treatment groups were compared against placebo.

For continuous efficacy variables (ADAS-cog, MMSE, CDR-SB, and QoL), a linear model was used to construct ANCOVA to compare the treatment groups: changes from baseline score measured against each subsequent visit (weeks 6, 12, 18, 24, and 30) to endpoint. The models contained factors for baseline score, treatment effect, center effect, treatment-by-center interaction, and random error. The overall treatment effects (difference in efficacy between the three treatment groups) were analyzed using type III sums of squares performed to determine statistical significance. In cases where differences existed, pairwise comparisons between active treatment and placebo were undertaken using Fisher's two-tailed least significant difference procedure.

The categorical efficacy variable, the CIBIC plus, was analyzed using the Cochran-Mantel-Haenszel test with RIDITS as the score option and included adjustments for center differences.

Comparability of the three groups for quantitative differences in continuous demographic variables (e.g., age, weight, height) was assessed using ANOVA models with factors for treatment and center. Comparability of the groups with regard to categorical variables such as race and sex was assessed using the Cochran-Mantel-Haenszel procedure with centers as strata.

Intragroup changes in vital signs (baseline versus endpoint) were analyzed using paired t-tests, and between treatment differences were detected by ANOVA. The analysis of adverse events was confined to treatment-emergent signs and symptoms (TESS) that began during or after administration of the first dose of study medication or became more severe during treatment. Events, recorded using investigator terminology, were grouped and coded into common terms using a modified COSTART dictionary.[26] Investigator assessment of relationship to treatment for all adverse events, serious and nonserious, was conducted under blinded conditions.

Table 1 *Summary of demographic characteristics of patients randomized to study treatments*

Characteristics	Treatment groups		
	Placebo (n = 162)	Donepezil 5 mg/d (n = 154)	Donepezil 10 mg/d (n = 157)
Age* (y)	72.6 ± 0.6	72.9 ± 0.6	74.6 ± 0.6†
(range)	(56–88)	(51–86)	(53–94)
Sex			
Male (%)	63 (39)	57 (37)	60 (38)
Female (%)	99 (61)	97 (63)	97 (62)
Race			
White (%)	153 (94)	146 (95)	150 (96)
African-American (%)	6 (4)	5 (3)	3 (2)
Other (%)	3 (2)	3 (2)	4 (3)
Screening CDR			
0.5 (%)	0	1 (1)‡	0
1.0 (%)	121 (75)	114 (74)	119 (76)
2.0 (%)	41 (25)	39 (25)	37 (24)
Screening MMSE*	19.2 ± 0.4	19.0 ± 0.4	18.9 ± 0.4

* Values are means ± SEM.
† The difference in mean age between the 10 mg/d donepezil treatment group and the placebo group was significant ($p = 0.03$).
‡ Patient was subsequently excluded as a protocol violation.

The incidences of TESS and treatment-emergent abnormal laboratory values (TEAVs) (i.e., newly occurring or clinically significant exacerbations of pre-existing abnormalities) were compared across treatment groups using Fisher's exact test.

All statistical analyses were performed using SAS version 6 (SAS Institute, Cary, NC). All hypothesis tests were two-sided, with analyses being significant if a ≤ 0.05 level was achieved.

Results. *Demographic characteristics.* Patient demographic characteristics did not differ between treatment groups, except for age (table 1). The mean age of the donepezil 10-mg/d group was 2 years older than the mean for the placebo group ($p = 0.03$). Other patient characteristics such as weight, height, and caffeine and alcohol use were similar between the groups (data not shown).

Efficacy assessment. As a consequence of the low discontinuation rate recorded in this trial, evaluable patient population and intent-to-treat (ITT) analyses gave results that were essentially the same. Further discussion of these results will report the more conservative ITT analyses.

Primary efficacy parameters: ADAS-cog. As indicated in figure 1, the mean ADAS-cog score for the placebo group actually improved after 6 weeks versus baseline but steadily worsened at each 6-week interval thereafter. This temporary improvement in placebo is consistent with the observation in trials of other antidementia agents and other CNS drugs (i.e. antidepressants).[27] There were no differences in pairwise comparisons between placebo versus the donepezil 5- and 10-mg/d group mean change

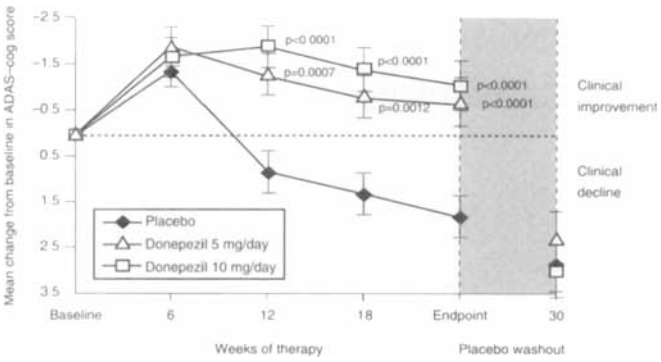

Figure 1. Mean (± SEM) change from baseline in ADAS-cog score for 5- and 10-mg/d-donepezil- and placebo-treated patients with mild to moderate Alzheimer's disease.

scores at the first 6-week visit. However, thereafter, the ADAS-cog performance for donepezil-treated patients did not deteriorate with time, thus generating a statistically significant treatment effect versus placebo at the 12-, 18-, and 24-week visits and at study endpoint (see figure 1).

Mean changes in ADAS-cog scores at study endpoint in the donepezil-treated groups revealed a dose-response relationship. An improvement of −0.67 and −1.06 in ADAS-cog scores from baseline was observed for the 5- and 10-mg/d-donepezil groups, respectively, whereas the placebo group deteriorated 1.82 points (table 2). Mean drug-placebo differences were −2.49 and −2.88 for the 5- and 10-mg/d dose groups, respectively ($p < 0.0001$) (see table 2, figure 1).

The percentages of patients in each group with poorer cognitive test performance on the ADAS-cog in the endpoint analysis relative to baseline were placebo, 42.3%; donepezil 5 mg/d, 20.3%; and donepezil 10 mg/d, 18.9%, suggesting that at least 80% of patients receiving donepezil did not experience cognitive worsening as compared with 57.7% of placebo patients over the 24 weeks of treatment (figure 2). Because no measurable decline in cognition (as assessed by ADAS-cog) is considered to be a clinical benefit in a progressive condition such as AD, treatment with donepezil provides obvious clinical benefit.

An improvement of four points or greater in ADAS-cog score versus baseline was seen in 26.8% of placebo, 37.8% of the 5-mg/d, and 53.5% of the 10-mg/d treated patients (see figure 2). Improvement of seven points or greater versus baseline at study endpoint was seen in 25.2% of the 10-mg/d-donepezil group, 15.4% of the 5-mg/d-donepezil group, and only in 7.8% of the placebo group.

Primary efficacy parameters: CIBIC plus. Beginning at the week 12 assessment and continuing throughout

***Table 2** Results (means at study endpoint) of pairwise comparisons for primary and secondary efficacy variables (ITT-LOCF analyses)*

	ADAS-cog			CIBIC plus		
	Placebo (n = 153)	Donepezil 5 mg/d (n = 152)	Donepezil 10 mg/d (n = 150)	Placebo (n = 152)	Donepezil 5 mg/d (n = 149)	Donepezil 10 mg/d (n = 149)
Primary efficacy variables						
Mean baseline score*†	27.28 ± 0.96	26.28 ± 0.96	27.41 ± 0.86	—	—	—
Endpoint: mean ADAS-cog change from baseline/CIBIC plus value at endpoint*	1.82 ± 0.49	−0.67 ± 0.51	−1.06 ± 0.51	4.51 ± 0.08	4.15 ± 0.09	4.07 ± 0.07
Drug-placebo difference		−2.49	−2.88		0.36	0.44
p (treatment vs. placebo)‡		<0.0001	<0.0001		0.0047	<0.0001
Mean change at 30 weeks*§	2.91 ± 0.57	2.29 ± 0.56	2.96 ± 0.64	4.73 ± 0.09	4.48 ± 0.10	4.78 ± 0.10
	MMSE			CDR-SB		
	Placebo (n = 154)	Donepezil 5 mg/d (n = 153)	Donepezil 10 mg/d (n = 150)	Placebo (n = 153)	Donepezil 5 mg/d (n = 154)	Donepezil 10 mg/d (n = 151)
Secondary efficacy variables						
Mean baseline score*†	19.40 ± 0.37	19.44 ± 0.38	19.17 ± 0.37	6.98 ± 0.19	7.11 ± 0.19	7.13 ± 0.19
Endpoint: mean change from baseline*	−0.97 ± 0.28	0.24 ± 0.29	0.39 ± 0.29	0.58 ± 0.14	−0.01 ± 0.14	−0.02 ± 0.14
Drug-placebo difference		1.21	1.36		0.59	0.60
p (treatment vs. placebo)		0.0007	0.0002		0.0008	0.0007
Mean change at 30 weeks*§	−1.18 ± 0.31	−0.40 ± 0.30	−0.97 ± 0.34	0.66 ± 0.16	0.21 ± 0.16	0.34 ± 0.18

* Values are means ± SEM.

† Mean baseline score at randomization.

‡ Despite the difference in age between the groups, the treatment by age interaction was not found to be significantly significant. An ANCOVA model where response = overall means + baseline score + age at baseline + treatment effect + site effect + random effect was used as the primary model to test for overall treatment effect using type III sums of squares.

§ Means are the change from baseline at 30 weeks after a 6-week, single-blind washout.

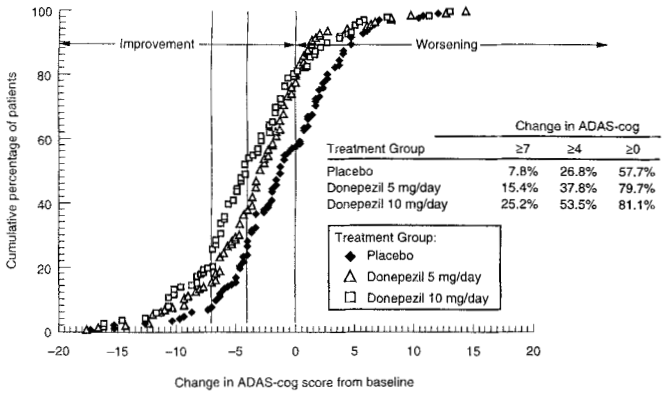

Figure 2. Cumulative percentage of patients with specified changes from baseline in ADAS-cog scores.

double-blind treatment, both the 5- and 10-mg/d-donepezil treatment groups exhibited improvement in global function relative to placebo ($p \leq 0.005$ at endpoint; figure 3). The differences in mean drug-placebo CIBIC plus scores at endpoint were dose dependent at 0.36 for the 5- and 0.44 for the 10-mg/d dosing groups. The strength of these results can be seen by examining the percentage of patients who were scored as improved on drug compared with placebo at study endpoint. Only 11% of placebo patients, as compared with 26% of the 5-mg/d and 25% of the 10-mg/d donepezil-treated patients were scored as improved (CIBIC plus ≤ 3). Overall, donepezil increased the number of treatment successes (CIBIC plus ≤ 4). Furthermore, donepezil reduced the number of treatment failures (CIBIC plus ≥ 5; $p = 0.0018$); the percentage of patients who had failed visits at least half the time were 45% in the placebo, 33% in the 5-, and 25% in the 10-mg/d-donepezil groups. After the 6-week-long, single-blind placebo washout, similar to the means of the ADAS-cog scores (see figure 1), the CIBIC plus ratings for both donepezil groups declined to levels that were not significantly different from the means of the placebo group (see figure 3), indicating that this beneficial effect of donepezil relies on its continued administration.

Secondary efficacy parameters. Donepezil treatment groups demonstrated a dose-dependent improvement in MMSE scores compared with placebo ($p \leq 0.0007$; figure 4) with mean drug-placebo differences of 1.21 for the 5- and 1.36 for the 10-mg/d-donepezil groups (see table 2).

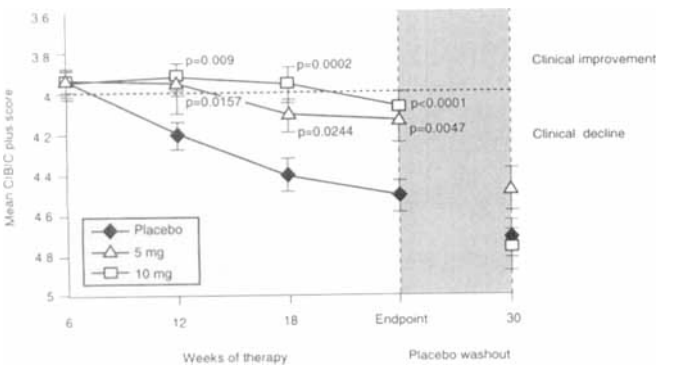

Figure 3. Mean (± SEM) CIBIC plus score for 5- and 10-mg/d-donepezil- and placebo-treated patients with mild to moderate Alzheimer's disease.

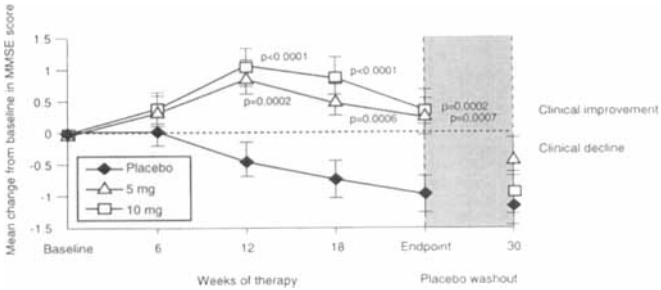

Figure 4. Mean (± SEM) change from baseline in MMSE score for 5- and 10-mg/d-donepezil- and placebo-treated patients with mild to moderate Alzheimer's disease.

Furthermore, improvements were observed in CDR-SB scores at weeks 18 and 24, plus at study endpoint ($p \leq 0.0008$; figure 5) with a mean drug-placebo difference for both the 5- and 10-mg/d-donepezil treatment groups of 0.6 (see table 2). Patient perceptions of their well-being as measured by the QoL scale showed a trend for improvement for both dose groups versus placebo by the 12-week visit and the improvement was sustained throughout the 18- and 24-week visits. However, only the 5-mg/d-dose group achieved significant improvement and this was only at week 24 ($p = 0.05$) (figure 6). Significant differences were not evident at study endpoint.

After the 6-week, single-blind placebo washout phase at the end of this study, scores on all measures declined to values that were not statistically different from placebo. There was no evidence of "overshoot" or decline in clinical state that was worse than that of patients who received placebo for the entire trial, suggesting that abrupt drug withdrawal did not cause exacerbation of symptoms or adverse effects. Interestingly, analyses of the CDR-SB data after placebo washout in this trial suggested residual benefits for both the 5- and 10-mg/d-donepezil groups when compared with the placebo group (see figure 5). However, this is not thought to signify any lingering pharmacodynamic activity of donepezil, especially because other efficacy parameters had returned to baseline values at the same time point, but rather the insensitivity of the assessment tool to quantify the degree of change.

Safety. The percentages of patients completing the study on their originally assigned treatment regimen were placebo, 80%; donepezil 5 mg/d, 85%; and donepezil 10 mg/d, 68%. The percentages of the patients in the groups

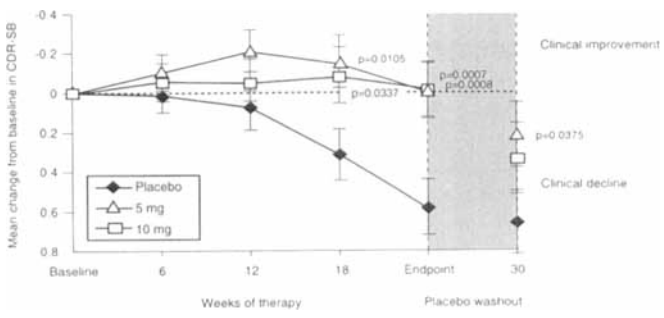

Figure 5. Mean (± SEM) change from baseline in CDR-SB score for 5- and 10-mg/d-donepezil- and placebo-treated patients with mild to moderate Alzheimer's disease.

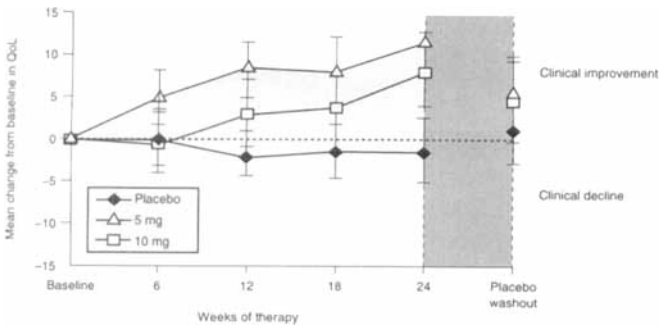

Figure 6. Mean (± SEM) change from baseline in QoL score for 5- and 10-mg/d-donepezil- and placebo-treated patients with mild to moderate Alzheimer's disease.

who discontinued the study because of an adverse event were placebo, 7%; donepezil 5 mg/d, 6%; and donepezil 10 mg/d, 16%. Only cholinergic-related effects, anticipated from the mode of action of this drug, were seen in significantly higher percentages of donepezil-treated patients as compared with the placebo group (table 3). Most of these adverse events were transient and of mild severity, except for nausea and vomiting that, although transient, were occasionally of moderate severity. The percentage of patients affected by cholinergic side effects was generally larger in the donepezil 10-mg/d group. The higher incidence of cholinergic side effects experienced in the 10-mg/d group was due to the forced, rapid titration schedule used in this study. In an open-label study of patients who received placebo in double-blind trials (n = 269), where the dose of donepezil was escalated to 10 mg/d after 4 to 6 weeks at 5 mg/d, the incidence of these cholinergic events

Table 3 *Number (%) of patients with treatment-emergent signs or symptoms*

Adverse event*	Placebo (n = 162)	Donepezil 5 mg/d (n = 154)	Donepezil 10 mg/d (n = 157)
Fatigue	3 (2)	8 (5)	12 (8)†
Diarrhea	11 (7)	14 (9)	27 (17)†
Nausea	6 (4)	6 (4)	26 (17)†
Vomiting	3 (2)	5 (3)	16 (10)†
Anorexia	3 (2)	3 (2)	11 (7)
Muscle cramps	1 (1)	9 (6)	12 (8)†
Dizziness	7 (4)	15 (10)	13 (8)
Rhinitis	4 (2)	1 (1)	9 (6)

* Treatment-emergent signs and symptoms were recorded by the COSTART body system and graded as mild, moderate, or severe (severity data not shown). All events are reported, whether or not considered related to treatment. Donepezil caused relatively little increase in adverse signs or symptoms as compared with placebo. Only cholinergic related effects were seen in significantly higher percentage of patients as compared with the placebo group. The percentage of patients affected was higher in the 10-mg/d group as compared with the 5-mg/d group, except for dizziness, which showed no relation to dose. Most of these events were mild or transient, except for nausea and vomiting, which were generally transient but of mild to moderate severity.

† $p \leq 0.05$. Overall p values were calculated only for preferred terms where the overall incidence rate was ≥5%.

was reduced to that experienced by the 5-mg/d-donepezil and placebo groups (Aricept, Eisai Inc., [donepezil hydrochloride tablets], package insert, Teaneck, NJ).

Two patients died during this study: a placebo patient of pulmonary embolus and a patient in the 10-mg/d-donepezil treatment group, whose cause of death was determined to be poorly defined infection or possibly metastatic cancer of the liver. Neither of these deaths were considered to be related to treatment. Thirty-one patients (6%) experienced one or more serious adverse event during the study or within 1 month of its termination, with most considered not related to the study drug (table 4). Slightly more patients experienced serious adverse events in the 10-mg/d-donepezil group (15 patients; 10%) than in the 5-mg/d-donepezil (7 patient; 5%) or placebo (9 patients; 6%) groups. The percentages of adverse events judged as possibly related to treatment was lowest for the 10-mg/d group (24%). No events were judged probably or definitely related to treatment.

TEAVs were uncommon in this study. Analysis of liver function tests (alanine transaminase, aspartate transaminase, alkaline phosphatase, total bilirubin, and albumin) demonstrated that the incidence of clinically significant TEAVs for patients with 5 or 10 mg/d donepezil did not differ statistically from patients treated with placebo. The only statistically significant difference in any laboratory test parameter was due to reports of a low level of hemoglobin in four patients in the 10-mg/d-donepezil group ($p = 0.0232$) as compared with no patients in the 5-mg/d-donepezil or placebo groups. However, in two of these patients, the low values were due to pre-existing conditions. Thus, for treatment-emergent abnormalities, there were no differences among the treatment groups.

AChE inhibition. The mean percentage inhibition of RBC AChE at 6 weeks in the 5-mg/d-donepezil treatment group was 63.7% and for the 10-mg/d-donepezil treatment group was 77.3%. Neither of these means changed significantly in the subsequent 6-week measurements during the treatment phase, indicating the pharmacodynamics of donepezil were stable over the course of the study. The relationship between plasma donepezil concentrations and percentage AChE inhibition is shown in figure 7. A few data points show a 0% inhibition of RBC AChE inhibition even though a high plasma donepezil concentration was achieved. These occasional disparities were due to errors in sample processing and shipping from the study sites. E_{max} for rbc AChE inhibition was 98.43% and the EC_{50} was 13.4 ng/mL donepezil.

Discussion. This 24-week trial confirms that donepezil is efficacious in treating symptoms of memory and cognitive loss in patients with mild to moderately severe AD. Patients treated with donepezil demonstrated improvements in cognitive function, as measured by the ADAS-cog, and in global clinical function, as measured by the CIBIC plus, relative to placebo. Benefits in the donepezil-treated groups were also found using the MMSE, CDR-SB, and to a lesser extent QoL, confirming that there were cognitive and functional improvements associated with donepezil treatment that were maintained throughout the double-blind treatment period. There is evidence of a dose-response effect, with the done-

***Table 4** Serious adverse events**

Donepezil dose	Serious adverse event (COSTART preferred terms)	Relationship to drug
Placebo	Cholelithiasis, nausea, vomiting	Not related
	Basal cell carcinoma	Not related
	Cerebrovascular accident†	Not related
	Infarct myocardial	Not related
	Pain chest, dyspnea, diaphoresis	Not related
	Ischemia myocardial,‡ syncope	Possibly related§
	Joint disorder	Not related
	Embolus pulmonary†	Not related‖
	Abdominal disturbance,† gastrointestinal disorder†	Possibly related
	Bronchitis	Possibly related§
5 mg/day	Basal cell carcinoma	Not related
	Infection	Not related
	Angina pectoris	Possibly related§
	Premature ventricular contractions,† syncope,† dizziness†	Possibly related§
	Infection, pyelonephritis,† renal failure†	Possibly related§
	Joint disorder†	Not related
	Accident, pulmonary collapse	Not related
10 mg/day	Hernia†	Not related
	Pneumonia	Not related
	Accident, fracture bone	Not related
	Head pressure,† blood pressure oscillatory,† drooling,† ataxia,† dysarthria†	Possibly related
	Agitation†	Possibly related§
	Hernia	Not related
	Creatinine serum increased	Not related
	Carcinoma†	Not related
	Accident, fracture bone, hypoxia	Possibly related
	Accident,† fracture bone†	Not related
	Carcinoma breast	Not related
	Nausea, vomiting, dehydration, thrombosis venous deep	Possibly related
	Death†	Not related
	Accident,† fracture bone†	Not related
	Cerebrovascular accident†	Not related
	Syncope†	Not related

* Treatment relationship assigned under double-blind conditions.
† Patient withdrew because of this serious adverse event.
‡ Patient withdrew because of myocardial ischemia and two non-serious adverse events: movement disorder and psychosis.
§ Sponsor judged event "not related."
‖ Sponsor judged event "possibly related."

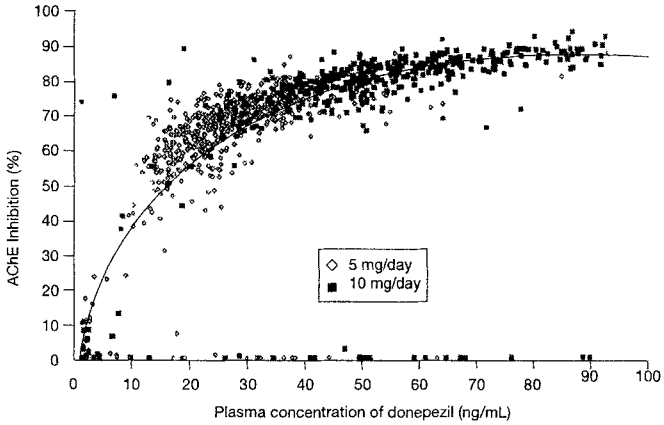

Figure 7. Correlation between plasma concentrations of donepezil and percentage RBC AChE inhibition (for all subjects at all visits where both determinants were evaluable).

pezil 10-mg/d patients showing somewhat greater improvement than the patients treated with donepezil 5 mg/d. Dose trend analyses using both Fisher's exact test and logistic regression indicate this dose-response is statistically significant ($p \leq 0.05$). The beneficial effects of donepezil became apparent at the 12-week visit and persisted with no decrease in magnitude at the 18- and 24-week visits and at study endpoint. The evaluable patient population and ITT analyses of these data gave very similar results, because a relatively small percentage of patients dropped out of this study for any reason.

Other ChE inhibitors have also shown efficacy in treating symptoms of AD but are often accompanied by significant or intolerable dose-related cholinergic side effects that have limited many patients' ability to continue treatment.[6,9,28,29] The high frequency of side effects may be partially attributed to peripheral inhibition of ChE by some agents. However, it may also be that the high rate of side effects is related to the high level of AChE inhibition necessary for positive cognitive effects and to rapid rates of fluctuation in AChE inhibition produced by these short-acting compounds. In comparison with the relatively short half-lives of some ChE inhibitors, the long half-life of donepezil (~70 hours) provides relative stability in the extent of AChE inhibition over the course of a day, which may also contribute to the relative reduction in cholinergic side effects seen with this drug. In addition to tolerance, the long half-life of donepezil allowed once-a-day dose administration in this trial. The convenience to caregivers probably contributed to the high levels of compliance and, in this study, to the high percentage of patients who completed the trial.

Previous studies of acridine-based ChE inhibitors have found evidence of hepatotoxicity in as many as 50% of patients, with levels three times greater than the upper limit of normal for alanine transaminase in 25% of patients.[6,9] As a consequence of the combined liability of cholinergic and hepatic side effects,

in a pivotal multicenter trial of tacrine versus placebo,[6] only 27% of patients in the highest dosage group (160 mg/d) were still available for an evaluable patient analysis at the end of the trial (30 weeks).

A relatively large treatment effect at 30 weeks was reported for the evaluable patient population in this tacrine trial, with the 160-mg/d-tacrine treatment group experiencing a 4.1-point improvement in ADAS-cog scores compared with placebo. For the ITT analysis, however, this improvement was reduced to approximately two points.[6] The 3.2-point mean at 24 weeks and the 2.9-point mean improvement seen by study endpoint in the ITT analysis of the high-dose donepezil (10 mg/d) group thus compares very favorably. To give perspective to the magnitude of these changes in ADAS-cog scores, the placebo cohort from this study had a 1.8-point deterioration, which is equivalent to an annualized rate of decline of approximately 3.9 points. This is lower than the average decline per year in untreated patients, because moderately severe untreated AD patients have been reported to decline by between 7 and 11 ADAS-cog points per year.[23,24] However, the instrument is not uniformly sensitive to change over the course of the disease with scores in mildly or severely demented patients increasing by only zero to five points per annum. Thus, performance of the placebo cohort in this study is consistent with these previous findings. For this reason, effect size in a controlled trial is more accurately determined as a percent of the annualized rate of decline of the placebo cohort of the trial. The treatment effect size for the two donepezil dose groups (drug-placebo difference expressed as a percent of placebo decline) represents about an 80% reduction of the annualized amount of cognitive decline in the placebo group.

A panel of experts convened by the FDA had previously suggested that an improvement of four points or more in ADAS-cog score with antidementia therapy would be considered a clinically significant effect.[30] Given that this criteria is influenced by the duration of the trial (given a long enough trial, no patient would have this benefit) and that it fails to consider the rate of decline in the corresponding placebo cohort (and, thus, the amount of movement expected on the ADAS-cog), it is not a meaningful way to judge the benefits of treatment. Approximately 40% of patients (160-mg/d group) completing the 30-week tacrine trial had ADAS-cog improvements of four points or greater. However, given the 73% dropout rate, only 12% of patients originally randomized to the 160-mg/d group achieved this standard of improvement. The change in placebo (in our trial) over 24 weeks is less than that seen in other studies. This may indicate that more mild patients were included here. However, 68% of the donepezil 10-mg/d patients completed this study and 53% of those completing had four points or greater improvement in ADAS-cog from baseline. Therefore, compared with the 12% from the tacrine study, three times as many patients, or 36%, achieved this level of benefit from donepezil.

It has been reported that ChE inhibitors (e.g., physostigmine and metrifonate) exhibit an inverted U-shaped curve when efficacy is plotted against percent inhibition of ChE and that clinical efficacy is obtained within a therapeutic window corresponding to 30 to 60% inhibition.[31-33] Hence, maximal clinical benefit would be gained at ~43% inhibition of AChE with actual worsening occurring at higher percentages of inhibition.[31-33] In the present study, the mean percentage inhibition of AChE, as measured by an RBC radioenzyme assay, was 63.7% for the 5-mg/d-donepezil group and 77.3% for the 10-mg/d group. The EC_{50} was seen at a plasma donepezil concentration of 13.4 ng/mL and a plateau of enzyme inhibition (80 to 90%) was attained at a higher plasma concentration. Thus, donepezil provides improved clinical efficacy even at relatively high levels of AChE inhibition.

The 10-mg/d-donepezil group, compared with placebo, showed the greatest change in mean ADAS-cog score versus placebo. Thus, it is possible that an even higher dosage of donepezil might further improve cognitive symptoms. However, doses of 10 mg/d produced rates of inhibition of AChE on the upper asymptote of the enzyme inhibition curve, suggesting that further increases in dose would provide only marginal increases in activity.

Twelve percent fewer of the 10-mg/d-donepezil treatment group completed the trial as compared with placebo, and the incidence of patients who discontinued the study because of adverse events was only 6% for the 5-mg/d group versus 16% for the 10-mg/d group. However, a rapid, forced titration schedule was used to increase the dosage in the 10-mg/d-donepezil group. Subsequent analysis from an open-label study of donepezil in donepezil-naïve patients has demonstrated that when a longer dosage titration schedule is used (escalation to 10 mg/d donepezil after 4 to 6 weeks at 5 mg/d), the occurrence of side effects is minimized. Indeed, by allowing achievement of steady-state concentrations at 5 mg/d before the elevation to 10 mg/d, the incidence of common adverse events was reduced, being comparable with that experienced by both the 5-mg/d-donepezil and placebo groups (Aricept [donepezil hydrochloride tablets], package insert). This is consistent with the side-effect profiles of many CNS agents, such as neuroleptics and tricyclic antidepressants, and is supported by similar findings from the tacrine trials. However, unlike the neuroleptics and tricyclics, no reverse titration is needed for donepezil. Abrupt discontinuation causes no adverse events and results in a gradual reduction of treatment benefit over 6 weeks.

The results of this trial demonstrate that donepezil improves both cognition and global function in patients with mild to moderately severe AD. It is well tolerated, with few patients having significant side effects. Donepezil would seem to have substan-

tial utility in treating patients with mild to moderate stage disease. The improvement in the CDR-SB scores in the donepezil-treated patients in this trial raises the possibility that donepezil may also positively affect functional activities of daily living. Future trials are necessary to determine if donepezil has significant effects in delaying deterioration or actually improving functional outcomes for AD patients. A drug that preserves function in patients' activities of daily living may help postpone the need for family and professional caring services, ultimately delaying nursing home placement and holding down the cost of caring for this increasing population.

Appendix

The Donepezil Study Group participants are as follows: Bruce Albala, Clinical Technologies Associates, Elmsford, NY; Barry Baumel, NeuroMedical Research Associates, Fort Lauderdale, FL; Gary Booker, LSU Medical Center, Shreveport, LA; James Dexter, University of Missouri, Columbia, MO; Mildred Farmer, Clinical Studies, St. Petersburg, FL; John P Feighner, Feighner Research Institute, San Diego, CA; Steven Ferris, NYU Medical Center, NY; Barry Gordon, Johns Hopkins University School of Medicine, Baltimore, MD; David G Gorman, Lovelace Science Resources, Inc., Albuquerque, NM; George Hanna, University of Virginia, Charlottesville, VA; Lindy E Harrell, The University of Alabama at Birmingham, Birmingham, AL; Richard Hubbard, Southwest Institute of Clinical Research, Rancho Mirage, CA; John Kennedy, Vanderbilt University Medical Center, Nashville, TN; F.C. Kinney, The University of Alabama at Birmingham, Birmingham, AL; James McCarthy, Clinical Studies, South Yarmouth, MA; Douglas W Scharre, Ohio State University, Columbus, OH; Frederick Schaerf, Clinical Studies, Fort Myers, FL; Lon Schneider, Hospital Place, Los Angeles, CA; Benjamin Seltzer, Tulane Medical School, New Orleans, LA; Alan Siegal, Center for Geriatric & Adult Psychiatry, Hamden, CT; Stuart R Stark, The Neurology Center, Alexandria, VA; Abbey Strauss, Clinical Studies, Boynton Beach, FL; Thomas M Walshe, Institute for Psychopharmacologic Research, Danvers, MA.

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Sulcal variability in the Alzheimer's brain

Correlations with cognition

M.S. Mega, MD, PhD; P.M. Thompson, MS; J.L. Cummings, MD; C.L. Back, PhD; M.L. Xu; S. Zohoori; A. Goldkorn, BS; J. Moussai, BS; L. Fairbanks, PhD; G.W. Small, MD; and A.W. Toga, PhD

Article abstract—We mapped the three dimensional (3D) extents and variability of selected sulci in the Alzheimer's brain and explored the relationship between sulcal pattern and patient's cognitive performance. High-resolution MRIs of 10 patients with probable Alzheimer's disease (AD) were linearly transformed into a standard "normalized" 3D atlas (known as the Talairach coordinate system) and, on each relevant slice, contours of the left and right Sylvian fissure, anterior and posterior calcarine, callosal, parietooccipital, and cingulate sulci and the floor of the temporal horn of the lateral ventricle were traced. These landmarks were chosen because of their relative invariant location across individuals and because they demarcate functional boundaries relevant in AD. The sulcal contours were resolved into two-dimensional surfaces that cut through a brain volume. All 10 patients' sulcal surfaces were averaged to determine their mean spatial locations in the Talairach coordinate system. The 3D spatial extents of each patient's sulci were compared with their disease severity based on neuropsychological performance. The 3D sulcal variability, within the "normalized" atlas space, ranged from 4.0 mm for the left callosal sulcus to 9.1 mm for the left Sylvian fissure. Significant correlations were found among the spatial extents for the posterior floor of the right temporal horn of the lateral ventricle ($r = -0.89$, $p < 0.001$ for vertical extent) and right anterior calcarine sulcus ($r = -0.75$, $p < 0.01$ for anterior-posterior extent) with copying ability of the Rey-Osterrieth Complex Figure; the right anterior calcarine also had a significant relationship ($r = -0.72$, $p = 0.02$ for anterior-posterior extent) with performance on the Block Design subtest from the Wechsler Adult Intelligence Scale–Revised. Verbal fluency performance measured by the Controlled Oral Word Association Test was significantly related to the left cingulate ($r = 0.91$, $p < 0.001$ for anterior-posterior extent, and $r = -0.82$, $p < 0.01$ for vertical extent) and right cingulate ($r = -0.72$, $p \leq 0.02$ for vertical extent) sulci. This exploratory study is the first to evaluate the relationship between 3D sulcal variability and cognition; our preliminary findings suggest that the 3D pattern of sulci in the AD brain is related to the severity of the disease as reflected by cognitive performance. In the Talairach brain atlas, sulcal variability, within an AD population, approaches 1 cm. This large variability requires correction when functional imaging data are transformed into the Talairach atlas space to "normalize" individual morphologic differences.

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The pathologic process in Alzheimer's disease (AD)—reflected by the concentration of neurofibrillary tangles (NFTs) and senile plaques—has a distinct regional predilection. The entorhinal cortex and subiculum/CA1 zone of the hippocampal formation are the first to manifest NFTs[1,2]; as the disease progresses, heteromodal association cortices are affected. The pathologic stages of AD follow the transi-

From the Department of Neurology, Laboratory of Neuro Imaging (Drs. Mega, Thompson, and Toga and M.L. Xu, S. Zohoori, A. Goldkorn, and J. Moussai), Alzheimer's Disease Center (Drs. Mega, Cummings, Back, Fairbanks, Small, and Toga), Department of Psychiatry and Biobehavioral Sciences (Drs. Cummings, Back, Fairbanks, and Small), and Center on Aging (Dr. Small), UCLA School of Medicine, Los Angeles, CA.

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Address correspondence and reprint requests to Dr. Arthur W. Toga, Laboratory of NeuroImaging, Department of Neurology, UCLA School of Medicine, 710 Westwood Plaza, Rm 4-238 Reed, Los Angeles, CA 90024-1769.

