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ABSTRACT Objective: To evaluate the efficacy and safety of donepezil for severe Alzheimer disease (AD). **Methods:** Patients with severe AD (Mini-Mental State Examination [MMSE] scores 1 to 12 and Functional Assessment Staging [FAST] scores ≥6) were enrolled in this multinational, double-blind, placebo-controlled trial at 98 sites. Patients were randomized to donepezil 10 mg daily or placebo for 24 weeks. Primary endpoints were the Severe Impairment Battery (SIB) and Clinician's Interview-Based Impression of Change-Plus caregiver input (CIBIC-Plus). Secondary endpoints included the MMSE, the Alzheimer Disease Cooperative Study–Activities of Daily Living–severe version (ADCS-ADL-sev), the Neuropsychiatric Inventory (NPI), the Caregiver Burden Questionnaire (CBQ), and the Resource Utilization for Severe Alzheimer Disease Patients (RUSP). Efficacy analyses were performed in the intent-to-treat (ITT) population using last post-baseline observation carried forward (LOCF). Safety assessments were performed for patients receiving ≥1 dose of donepezil or placebo. **Results:** Patients were randomized to donepezil (n = 176) or placebo (n = 167). Donepezil was superior to placebo on SIB score change from baseline to endpoint (least squares mean difference 5.32; $p = 0.0001$). CIBIC-Plus and MMSE scores favored donepezil at endpoint ($p = 0.0473$ and $p = 0.0267$). Donepezil was not significantly different from placebo on the ADCS-ADL-sev, NPI, CBQ, or RUSP. Adverse events reported were consistent with the known cholinergic effects of donepezil and with the safety profile in patients with mild to moderate AD. **Conclusion:** Patients with severe AD demonstrated greater efficacy compared to placebo on measures of cognition and global function. **NEUROLOGY 2007;69:459–469**

Patients who progress to the severe stage of Alzheimer disease (AD) have markedly diminished cognitive and functional abilities, reduced social interaction, and their capacity to perform instrumental activities of daily living (ADLs) is significantly compromised. While basic ADLs can be carried out to varying degrees, impairments in such ADLs as bathing and toileting are common.[1] Although patterns of decline are well documented across the stages of AD, few studies have detailed the cognitive and functional abilities that may be retained by severe-stage patients, particularly if they receive appropriate stimulation and care.

It is estimated that there were 4.5 million Americans with AD in 2000 and about 21% of these cases were classified as severe; both of these figures are predicted to increase substantially over the next half century.[2] Persons with AD rely increasingly on their caregivers as the disease progresses.[3] Indeed, unpaid caregiver time is one of the greatest costs associated with community-dwelling patients with severe AD. However, the largest driver of direct costs is institutionalization, with care-related cost for patients with severe AD considerably higher than for patients with milder forms of the disease.[4]

Supplemental data at www.neurology.org

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In the United States, the first approved treatment for severe AD was memantine, an *N*-methyl-D-aspartate (NMDA) receptor antagonist.[5] Data from randomized, double-blind, placebo-controlled studies including patients with severe AD[6,7] have indicated that the cholinesterase inhibitor donepezil also provides treatment benefits for patients with severe AD. These data led to the recent approval of donepezil for severe AD by the US Food and Drug Administration.

There have been arguments against treating patients with severe AD.[8] Certainly, reversing cognitive and functional decline during the severe stage of AD is not a realistic treatment goal. However, maintenance or less than expected decline might be a worthwhile treatment goal because it may help to keep patients at home longer —something that patients and caregivers often desire and which delays the costs of institutionalization. The present study investigated the potential treatment benefits of donepezil in community-dwelling patients with severe AD.

METHODS

Study design. This study was a 24-week, multinational, randomized, double-blind, placebo-controlled trial of patients with severe AD conducted in 98 centers in the United States, Canada, France, the United Kingdom, and Australia. Verbal consent was obtained from the patient, if capable, but written informed consent was always obtained from the patient's caregiver or legal representative prior to enrollment. This study was conducted according to the Declaration of Helsinki. A total of 343 patients were randomized to either donepezil (n = 176) or placebo (n = 167) according to a computerized randomization schedule generated by Almedica Service Corp. from May 1, 2001, through January 17, 2005. The double-blinding method consisted of a medication kit for each patient containing three blister cards with all medication tablets for the 24 weeks of treatment. Blinding was maintained on a tear-off portion of the label for each individual patient kit. The investigator removed the label and attached it, without opening it, to the case report form before dispensing the medication card to the patient. Patients randomized to study medication received one tablet of donepezil 5 mg daily and one placebo tablet for 6 weeks and then two 5-mg tablets (10 mg daily) thereafter. Patients randomized to placebo received two placebo tablets for the entire double-blind phase of the study. The first dose of study medication was administered in the clinic at the baseline visit. All subsequent doses were administered every evening, just before bedtime. Placebo and donepezil tablets were identical in appearance. In consideration of tolerability, the clinician was permitted to reduce the study medication to one blinded tablet per day if necessary after week 6.

Patients. All patients were ambulatory or ambulatory-aided (cane, walker, or wheelchair) men or women aged at least 50 years diagnosed with probable AD consistent with the *Diagnostic and Statistical Manual of Mental Disorders*, 4th edition[9] and the National Institute of Neurological and Communicative Disorders and Stroke and Alzheimer Disease and Related Disorders Association criteria.[10] At screening the patients were required to have a Mini-Mental State Examination (MMSE)[11] score between 1 and 12 (inclusive), a modified Hachinski Ischemic[12] score of ≤6, and a Functional Assessment Staging (FAST)[13] score of ≥6 for inclusion in the study. Patients in skilled nursing homes or who were expected to require skilled nursing home care within the next 6 months were excluded. All patients were required to have a reliable caregiver with whom they had direct contact for a minimum of 3 days per week (at least 4 hours per day during waking hours). Patients with stable type 1 or type 2 diabetes, controlled hypertension, right bundle branch block, a pacemaker, thyroid disease that was stable (i.e., euthyroid) on treatment, or a seizure disorder that was stable (i.e., no treatment change for at least 3 months and no seizure within 6 months) could be included in the study. All patients were able to swallow tablets, as no crushing of the study tablets was allowed.

Patients with a known sensitivity to piperidine derivatives or cholinesterase inhibitors were excluded from the study as were patients with clinically significant obstructive pulmonary disease or asthma left untreated (i.e., uncontrolled) within 3 months of study entry, patients who had had a hematologic or oncologic disorder within the past 2 years, and patients with significant active gastrointestinal, renal, hepatic, endocrine, or cardiovascular disease. Any patient with a current primary psychiatric diagnosis other than AD, including major depressive disorder, was excluded from the study. Patients with dementia complicated by other organic disease or dementia due to tertiary syphilis were excluded. Also excluded were patients with a known or suspected history of alcohol or drug abuse within the past 10 years. Patients taking most prescription or over-the-counter medication with known psychotropic activity or cholinergic or anticholinergic effects were excluded.

The protocol specified the following restrictions on prior and concomitant medication use: 1) loxapine, haloperidol, risperidone, olanzapine, quetiapine, zolpidem, oxazepam, lorazepam, and selective serotonin reuptake inhibitor antidepressants were allowed provided that either the patient had been taking a stable dose for at least 6 weeks before the baseline visit and would need to remain on the same dosing regimen for 4 weeks after the baseline visit; or, if not taking such medication at baseline, it was not started for at least 4 weeks after baseline; 2) cyclobenzaprine, propoxyphene, and cold preparations containing antihistamines or sympathomimetic amines were allowed for 3 days out of every 2 weeks but not within 48 hours of a testing visit. Patients were allowed to have been previously treated with cholinesterase inhibitors, memantine, or propentofylline, provided it was discontinued at least 3 months before screening. Putative cognitive enhancers (e.g., gingko, vitamin E, or selegiline) were not encouraged but were allowed, provided that the dose was stable for 3 months before screening and during the study. Experimental AD treatments must have been discontinued 1 month or five drug half-lives before screening, whichever was longer.

Primary efficacy measures. The primary efficacy measures for the study were the Severe Impairment Battery (SIB)[14,15] and the Clinician's Interview-Based Impression of Change-Plus caregiver input (CIBIC-Plus).[16] Conducted at baseline and at study weeks 8, 16, and 24, the SIB is a comprehensive evaluation of cognitive dysfunction in patients with more advanced AD. It is designed to evaluate the following domains: orientation, attention, language, praxis, visuospatial ability, construction, memory, orientation to name, and social interaction. The SIB includes 40 items and has a range of possible scores from 0 to 100, with lower scores indicating greater impairment.

The CIBIC-Plus is an independent global assessment of the patient's response to treatment. It uses a semistructured interview covering four domains (general, mental/cognitive state, ADLs, and behavior) that is conducted as separate interviews with the caregiver and the patient. Evaluations were made at weeks 8, 16, and 24 to quantify any changes from the Clinician's Interview-Based Impression of Severity (CIBIS-Plus), which covers the same domains and is administered at baseline. CIBIC-Plus scores range from 1 to 7 on a Likert scale, with lower scores indicating improvement, a score of 4 indicating no change, and higher scores indicating deterioration from baseline.

Secondary efficacy parameters. The secondary efficacy measures included the Alzheimer Disease Cooperative Study–Activities of Daily Living–severe version (ADCS-ADL-sev),[17,18] the Neuropsychiatric Inventory (NPI),[19] the MMSE,[11] the Caregiver Burden Questionnaire (CBQ), and the Resource Utilization for Severe Alzheimer Disease Patients (RUSP).

The ADCS-ADL-sev is administered as a caregiver interview and is a 19-item scale that measures basic and instrumental ADLs appropriate in this patient population. Scoring is from 0 to 54, with lower scores indicating greater functional impairment. The NPI assesses behavior in dementia patients, including delusions, hallucinations, depression/dysphoria, anxiety, agitation/aggression, euphoria, disinhibition, irritability, apathy, aberrant motor activity, sleep, and appetite. It is administered as a structured caregiver interview, with scores ranging from 0 to 144 and higher scores indicating greater impairment. The MMSE is a brief test that assesses the patient's cognitive status, orientation, and memory. Scores range from 0 to 30, with lower scores indicating greater cognitive impairment. The CBQ evaluates the time and the stress associated with assisting the patient with performance of daily tasks; lower scores indicate less burden for the caregiver. The RUSP provides an assessment of the resources used by the patient, including accommodation, visits to the emergency room, hospitalizations, visiting nurse, home health aid, daycare, respite care, and meal delivery services; lower scores indicate less utilization of resources. All secondary measures were given at baseline and at weeks 16 and 24 of the study.

Safety. Safety was assessed by monitoring adverse events (AEs) through the course of the study. AEs were considered serious (SAEs) when death occurred, life was threatened, hospitalization or prolonged hospitalization was required, or a significant disability occurred. Vital signs were recorded at all visits. Medical history was obtained at screening. Complete physical examinations, neurologic examinations, electrocardiograms (ECGs), and clinical laboratory tests were performed at screening and week 24 of the study. A shorter physical assessment was done at baseline, week 8, and week 16. The Unified Parkinson Disease Rating Scale (UPDRS) motoric domain was used to assess extrapyramidal motor function. Significant vascular disease was ruled out at screening by the modified Hachinski Ischemia scale (scores $\leq$6) and by neuroimaging (CT or MRI scan). Concomitant medication use was monitored throughout the study.

Statistical analysis. Sample sizes and power calculations were generated according to the primary efficacy endpoints of the study (SIB and CIBIC-Plus). A sample size of 312 patients was originally estimated to give a power of 90% to show a 0.45 point improvement on the CIBIC-Plus and a power of 97% to show a 7.2 point improvement on the SIB change from baseline, compared to placebo; assuming a 5% type-I error rate and SD of 1.22 and 16.3 for the CIBIC-Plus and SIB. To account for a 70% completion rate, the sample size was increased to 440. After a blinded 50% data review revealed that a lower than expected percent of patients would be excluded from the intent-to-treat (ITT) population, an amendment decreased the sample size estimate to approximately 350 patients (175 per treatment group).

The primary efficacy variables were 1) change from baseline to endpoint visit in the SIB total score and 2) CIBIC-Plus scores at the endpoint visit. The primary efficacy analyses were based on the least squares (LS) mean change from baseline to endpoint of the ITT population using a last observation carried forward (LOCF) analysis at week 24 of the study. The ITT population consisted of all patients who were randomized, received at least one dose of donepezil or placebo, and had a baseline as well as at least one post-baseline efficacy value for the variable being analyzed. Observed case (OC) analyses were also performed at study weeks 8, 16, and 24 for the continuous variables.

Analysis of covariance factoring in treatment, pooled center, and baseline was used to evaluate treatment differences at each visit after baseline for SIB, ADCS-ADL-sev, NPI, MMSE, CBQ, and continuous variables of the RUSP. Summary statistics by visit were performed for continuous variables (N, mean, standard error [SE], min, max, LS mean, and SE of LS mean). All statistical tests were two-tailed and were carried out at the 0.05 level of significance.

The CIBIC-Plus and categorical variables of the RUSP were analyzed by the Cochran-Mantel-Haenszel test, adjusted for pooled center at week 24 LOCF. The CIBIC-Plus, a seven-category Likert-type scale, was collapsed from seven to three categories (1 to 3 = improved; 4 = no change; 5 to 7 = worsened) due to insufficient numbers of patients in categories 1, 2, and 7. In addition, it has been demonstrated that collapsing categories significantly improves inter-rater reliability.[20,21] The mean CIBIC-Plus score (full seven-point scale) was also analyzed as a continuous variable. In additional post hoc analyses, the CIBIC-Plus was adjusted for baseline severity (CIBIS-Plus score).

The safety analysis was performed in the safety population, which consisted of all patients who were randomized and took at least one dose of study medication. All AEs were recorded regardless of whether they were considered to be related to study medication. AEs were to include treatment-emergent symptoms and treatment-emergent abnormal values for laboratory parameters.

All statistical analyses were performed by SAS version 6.12 (SAS Institute Inc., Cary, NC) or a more recent version.

Table 1 Summary of patient characteristics for all randomized patients at baseline

	Treatment group		
	Donepezil (n = 176)	Placebo (n = 167)	Overall (n = 343)
Age, y, mean (SD)	78.0 (8.04)	78.0 (8.20)	78.0 (8.10)
Age category, y, n (%)			
<65	12 (6.8)	10 (6.0)	22 (6.4)
65–74	34 (19.3)	43 (25.7)	77 (22.4)
75–84	105 (59.7)	75 (44.9)	180 (52.5)
≥85	25 (14.2)	39 (23.4)	64 (18.7)
Sex, n (%)			
Male	48 (27.3)	54 (32.3)	102 (29.7)
Female	128 (72.7)	113 (67.7)	241 (70.3)
Race, n (%)			
Black	24 (13.6)	16 (9.6)	40 (11.7)
White	134 (76.1)	127 (76.0)	261 (76.1)
Hispanic	15 (8.5)	21 (12.6)	36 (10.5)
Native American	0 (0.0)	1 (0.6)	1 (0.3)
Asian/Pacific	2 (1.1)	2 (1.2)	4 (1.2)
Other	1 (0.6)	0 (0.0)	1 (0.3)
Living arrangements, n (%)			
Lives alone	11 (6.3)	14 (8.4)	25 (7.3)
Lives with caregiver	137 (77.8)	126 (75.4)	263 (76.7)
Lives with relative/friend	11 (6.3)	10 (6.0)	21 (6.1)
Assisted living facility	15 (8.5)	13 (7.8)	28 (8.2)
Adult/senior residence/retirement home	2 (1.1)	4 (2.4)	6 (1.7)

RESULTS **Patient demographics and baseline values.** A total of 543 patients were screened. Of those screened, 343 patients were randomized into either the donepezil treatment group (n = 176) or placebo group (n = 167). The treatment groups were similar with respect to age, race, sex, living arrangement, and prior use of a cholinesterase inhibitor, memantine, or propentofylline. Baseline demographic characteristics are summarized in table 1. Most patients lived in the community (76.7% lived with a caregiver). The remainder lived in assisted living facilities or retirement homes (but not full skilled nursing homes). There were also no significant differences between groups on screening and baseline neuropsychological and cognitive test scores (table 2). The mean MMSE score was 7.5 for the donepezil group and 7.4 for the placebo group. In the donepezil group 30.7% of patients scored between 1 and 5 and 68.8% of patients scored between 6 and 12 on the MMSE at screening (vs 30.5% and 68.3% of the placebo group). The majority of patients had FAST scores of 6A-6E (86.0% of donepezil group and 85.8% of placebo group). The mean Hachinski score was 0.7 for the donepezil group and 0.9 for the placebo group.

Almost all of the patients (90.3% of donepezil and 94.0% of placebo patients) were using concomitant medications during the study. More than 20% of patients in either group were taking antiplatelet agents. The most common concomitant medications taken during the study (>10% in either group) included acetylsalicylic acid, multivitamins, tocopherol, risperidone, paracetamol, furosemide, levothyroxine sodium, and ascorbic acid. Concomitant medication use is described in table E-1 on the *Neurology* Web site at www.neurology.org. Approximately two thirds (61.2%) of the patients (58.5% of donepezil and 64.1% of placebo patients) were treatment-naïve for a cholinesterase inhibitor, memantine, or propentofylline. The category of psychotropic medications with the most frequent use at baseline, as well as the category most frequently used during the study, was selective serotonin reuptake inhibitors (donepezil 10.8%, placebo 16.2% at baseline; donepezil 14.8%, placebo 19.2% during the study). All other categories of psychotropic medi-

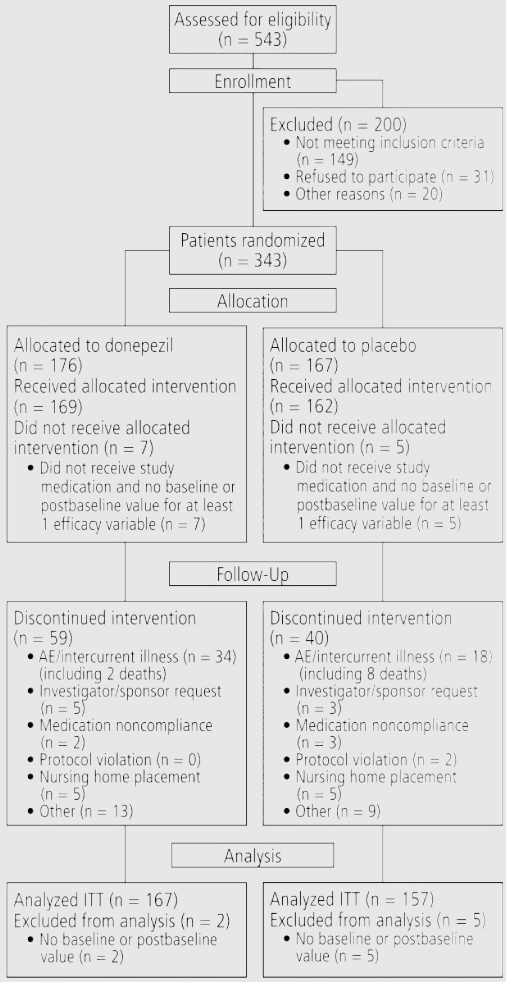
Table 2 Neurologic and cognitive test scores for all randomized patients at screening

	Treatment group	
Assessment	Donepezil (n = 176)	Placebo (n = 167)
Modified Hachinski total score, mean (SD)	0.7 (0.96)	0.9 (1.07)
MMSE score, mean (SD)	7.5 (3.25)	7.4 (3.57)
MMSE score distribution, n (%)		
1–5	54 (30.7)	51 (30.5)
6–12	121 (68.8)	114 (68.3)
>12	1 (0.6)	2 (1.2)
FAST total score, n (%)		
5	3 (1.7)	2 (1.2)
6.A–6.E	153 (87.0)	143 (85.8)
7.A–7.D	20 (11.3)	22 (13.2)

cations were used at a lower frequency and the difference in use between the treatment groups was no more than 5 to 6%.

Overall, 66.5% of patients in the donepezil group and 76.0% of patients in the placebo group completed the study (figure 1). The most common reason for discontinuation was AEs/intercurrent illness: 19.3% of donepezil patients and 10.8% of placebo patients discontinued for this reason. The maximum dose of 10 mg/day was maintained by 85% of patients in the donepezil group at study endpoint.

Figure 1 Patient disposition



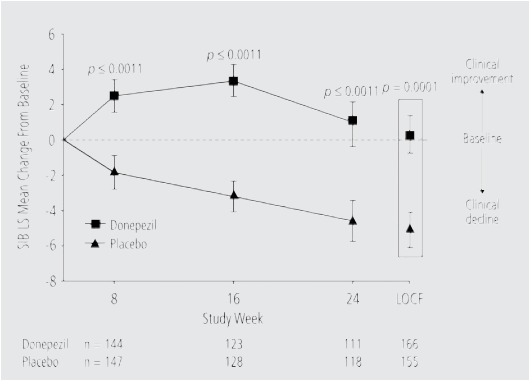
AE = adverse event; SAE = serious AE; ITT = intent to treat.

Primary efficacy measures. At baseline, mean total SIB scores were similar for both treatment groups (donepezil: 64.6; placebo: 65.2) with the donepezil group ranging from 5 to 97 (2 patients scored ≥95 and 1 patient scored ≤5) and the placebo group ranging from 4 to 100 (5 patients scored ≥95 and 2 patients scored ≤5). When comparing the two treatment groups, donepezil was superior to placebo at all time points and at week 24 LOCF (figure 2). The range of responses (cumulative percentage of patients by the actual changed score from baseline) showed 63.3% of donepezil patients had improvement or no change from baseline at week 24, compared with 39.4% of placebo patients. The effect size for the SIB (using Cohen's *d*) was 0.4145.

Figure 3 illustrates the range and breadth of deficits that contributed to the overall decline in mean SIB score in the placebo group. In contrast, donepezil-treated subjects improved vs their own baseline in five of the nine domains (memory, language, attention, praxis, and orienting to name) and were essentially unchanged in one (orientation). In the remainder (social interaction, visuospatial function, and construction), they showed less decline than the placebo group. This post hoc analysis suggests the consistency of the benefit vs placebo as shown in the overall mean treatment difference, although some domains appear more responsive than others.

Mean change from baseline to endpoint in the intent-to-treat (ITT) population.

Figure 2 Severe Impairment Battery (SIB)



The distribution of CIBIC-Plus scores in the extreme categories was found to be sparse. Therefore, the categories were collapsed from seven to three (improved, no change, worsened). The collapsed category analysis, adjusted for pooled site, revealed differences in favor of donepezil in the ITT population at week 24 LOCF ($p = 0.0473$; figure 4). The OC analysis at week 24 was also in favor of donepezil ($p = 0.0409$), which would argue against differential dropout as the explanation for the positive effect.

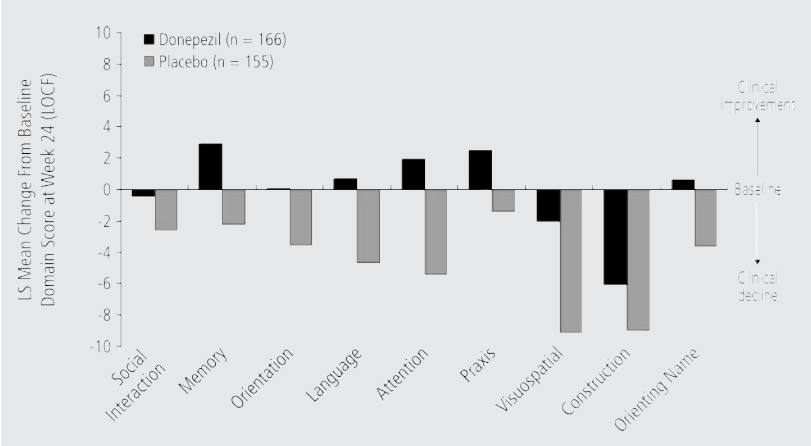
The CIBIC-Plus analysis on collapsed categories adjusted for baseline severity (CIBIS-Plus) score showed differences favoring donepezil over placebo for the ITT population at week 24 LOCF ($p = 0.0156$). The OC analysis at week 24 also demonstrated differences in favor of donepezil ($p = 0.0226$).

The seven-category analysis of CIBIC-Plus, adjusted for baseline severity (CIBIS-Plus) score, favored donepezil over placebo ($p = 0.0476$) for the ITT population at week 24.

When the CIBIC-Plus was analyzed as a continuous variable, mean scores were significantly different between donepezil and placebo groups, with a treatment difference in favor of donepezil in the week 24 LOCF and OC analyses (table 3). The effect size for the CIBIC-Plus (using Cohen's *d*) was 0.2048.

Individual domain analysis mean change from baseline to endpoint in the intent-to-treat (ITT) population.

Figure 3 Severe Impairment Battery (SIB)



Secondary efficacy measures. As shown in table 3, in the week 24 LOCF analysis, the donepezil group demonstrated significant improvement from screening to endpoint on the MMSE compared with placebo ($p = 0.0267$). The OC analysis at week 24 also showed a significant difference in favor of donepezil ($p = 0.0409$).

On the ADCS-ADL-sev, at week 24, both the donepezil group and the placebo group declined from baseline. The treatment difference at week 24 was not significant for either the LOCF or OC analysis (table 3).

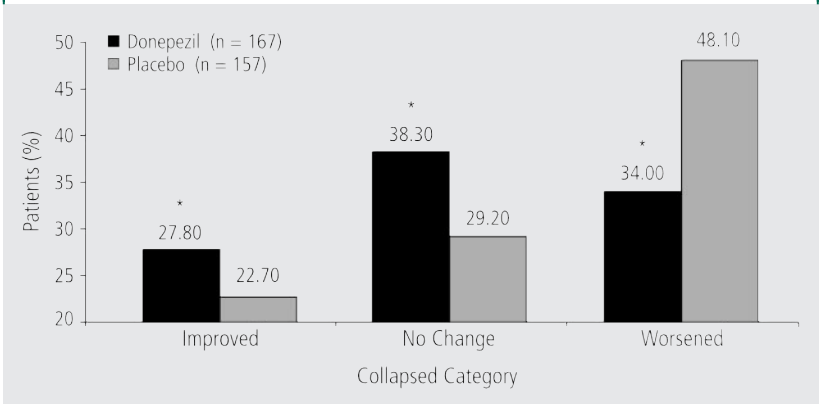
On the NPI, the LOCF analysis showed improvement from baseline in both groups. However, at week 24, changes in NPI scores were not significantly different from one another (table 3). The results for the OC analysis at week 24 were similar, except that the placebo improvement was greater than observed in the LOCF analysis (table 3).

On the CBQ stress measure, the reported levels of distress associated with assisting with various ADLs were generally very low (<1 where 1 = mild distress) and showed no significant change from baseline for either group. Similarly, the average time spent assisting with all ADLs was <6 hours for both groups, and the change at endpoint was an increase of about a half hour for both groups, which was not significantly different from baseline. The various elements of the RUSP also had low average responses with little movement from baseline and no significant differences.

Safety measures. Approximately three quarters of patients in this study experienced an AE (70.1% [n = 117] of placebo patients and 79.5% [n = 140] of donepezil patients). Most AEs (73.6%) were rated as mild or moderate. Placebo patients were more likely to experience severe AEs (15.6% [n = 26] of placebo vs 10.8% [n = 19] of donepezil patients). Placebo patients also reported more SAEs than donepezil patients (15.0% [n = 25] vs 11.4% [n = 20]). Two patients in the donepezil group (1.1%) and eight patients in the placebo group (4.8%) experienced an AE that led to death. None of the events leading to death was considered to be related to the study medication. The two deaths in the donepezil group were a result of a cerebral hemorrhage and respiratory failure and were not considered treatment related.

Patients in the donepezil group were more likely than patients in the placebo group to expe-

Figure 4 Clinician's Interview-Based Impression of Change-Plus (CIBIC-Plus) scores (collapsed categories) for the intent-to-treat (ITT) population at week 24 last observation carried forward (LOCF)



*$p = 0.0473$; p Values are obtained from a Cochran–Mantel–Haenszel row means score test (modified ridit score) of treatment difference with pooled site as a stratifying factor.

rience an AE considered related to study medication (42.0% [n = 74] vs 30.5% [n = 51]). These AEs included diarrhea, nausea, vomiting, anorexia, and agitation. The most common AEs reported by ≥5% of patients in the donepezil group and at twice the rate of the placebo group were diarrhea, insomnia, nausea, infection, urinary incontinence, and pain (table 4).

Donepezil patients were also more likely than placebo patients to reduce the study drug dose due to an AE (2.3% vs 1.2%). The most common AEs leading to discontinuation included anorexia, agitation, pneumonia, and somnolence.

There was no clinically meaningful change in laboratory tests from screening to week 24 in either treatment group. There was also no significant change in vital signs, including systolic or diastolic blood pressure, pulse rate, and temperature, from baseline to week 24 of the study. A similar number of patients in the donepezil group and the placebo group showed a shift in ECG findings at the end of treatment (7.9% vs 8.7%). Clinically significant shifts in ECG from normal values at screening to abnormal values at end of treatment occurred in 0.6% of both the donepezil and placebo groups. There was no trend in worsening in either treatment group on the motoric component of the UPDRS.

DISCUSSION The findings of the present study provide further evidence that donepezil benefits cognition and global function in patients with severe AD. The first prospective study to demonstrate such benefits was a recently published 6-month study conducted in nursing homes in Sweden.[7] Patients in that study had severe AD with a mean MMSE score of approximately 6 and more than 80% had a FAST score of 6c or higher. Results from the SIB demonstrated a mean improvement for the donepezil group, while scores in the placebo group declined. The other primary endpoint in the study was the ADCS-ADL-sev, which showed significantly less decline for the donepezil group than for the placebo group.[7] Another recent study also reported clinical benefits for patients with more severe AD.[6] These were results of post hoc analyses from an earlier study using a cohort with MMSE scores between 5 and 12 (inclusive); the findings showed that patients given donepezil performed significantly better than those given placebo on measures of cognition, function, behavior, and global function.[6]

The present multinational study was the first to evaluate donepezil in an exclusively severe cohort of community-dwelling AD patients and demonstrated efficacy for donepezil on measures of cognition and global function in patients with severe AD. Benefits over placebo were not evident on measures of ADL and behavior in this population. These patients were clinically characterized as having severe disease and had a mean baseline MMSE score of 7.4; more than 50% had a FAST score of 6c or greater.

This study demonstrated that patients with severe AD maintained cognitive function with donepezil treatment for at least 6 months, as evidenced by a significant treatment effect on the SIB compared with a decline of approximately 10% from baseline in patients receiving placebo. The course of decline seen in the placebo group is less than the decline on the SIB over a 6-month period in untreated patients with severe disease (about 15 points), as reported by the AD Cooperative Study Group.[14] This difference is likely explained by the differing characteristics of the two study populations, particularly the mix of degrees of severity, and possibly also by the testing schedule. Nonetheless, it is interesting to contrast the pattern of SIB improvement from baseline for the donepezil group over 6 months with the pattern of decline of untreated patients, such as those reported by the Alzheimer Disease Cooperative Study Group.[14] Likewise, it is interesting to look at the pattern of responses in a recently published memantine trial.[22] In that study, the active treatment group declined by about four points at 28 weeks, while the placebo group declined by about 10 points. While, again, there are differences in patient populations and trial design that limit direct comparisons, these results reinforce what appears to be a distinct efficacy profile for donepezil on the SIB in severely ill patients.

The overall functional status as measured by the CIBIC-Plus in the global domains of general

Table 3 Primary and secondary outcome measures for the ITT population

			LS mean change from baseline at week 24, score change (SE)					
	Baseline, mean (SE)		OC analysis			LOCF analysis		
Outcome measure	Donepezil	Placebo	Donepezil	Placebo	*p*	Donepezil	Placebo	*p*
SIB*	64.6 (1.76), n = 167	65.2 (1.95), n = 156	0.97 (1.17), n = 111	−4.62 (1.16), n = 118	0.0008	0.19 (0.97), n = 166	−5.13 (1.01), n = 155	0.0001
CIBIS-Plus/CIBIC-Plus†‡	5.1 (0.07), n = 166	5.1 (0.07), n = 156	4.10 (0.11), n = 109	4.32 (0.11), n =116	0.0323	4.11 (0.10), n = 162	4.45 (0.10), n = 153	0.0168
MMSE§	7.5 (0.25), n = 167	7.5 (0.28), n = 157	0.76 (0.31), n = 111	0.02 (0.30), n = 119	0.0409	0.65 (0.27), n =150	−0.03 (0.28), n = 141	0.0267
ADCS-ADL-sev¶	27.3 (0.92), n = 162	26.7 (1.14), n = 152	−1.83 (0.63), n = 104	−1.73 (0.62), n = 113	0.9120	−1.82 (0.54), n = 151	−2.53 (0.56), n = 140	0.3574
NPI‖	22.7 (1.60), n = 166	22.2 (1.55), n = 157	−1.79 (1.44), n = 110	−5.50 (1.42), n = 119	0.0682	−1.91 (1.33), n = 153	−3.31 (1.38), n = 144	0.4612

*p Values for the Severe Impairment Battery (SIB) were obtained from an analysis of variance (ANOVA) model with baseline included as a covariate in the model change = treatment + pooled site.
†Baseline values shown are the mean Clinician's Interview-Based Impression of Severity (CIBIS-Plus) scores (SE); week 24 values shown are the LS mean Clinician's Interview-Based Impression of Change-Plus caregiver input (CIBIC-Plus) scores (SE) analyzed as a continuous variable and represent the clinician's impression of change from the baseline CIBIS-Plus evaluation; these values do not represent a numerical change from the baseline CIBIS-Plus score; *p* value for the OC analysis was obtained from an analysis of covariance (ANCOVA) with baseline (CIBIS-Plus) included as a covariate in the model change = treatment + pooled site + treatment by covariate; *p* value for the LOCF analysis was obtained from an ANCOVA with baseline (CIBIS-Plus) included as a covariate in the model change = treatment + pooled site + treatment by pooled site.
‡CIBIC-Plus was also analyzed as a categorical variable using the Cochran–Mantel–Haenszel test stratified by pooled center. Seven categories were collapsed to three categories (1 to 3 = improved; 4 = no change; 5 to 7 = worsened) because sparsity in some of the extreme cells (1, 2, and 7) increased the variability and made interpretation difficult; the resulting *p* value was 0.0473. For completeness and potential future meta-analytic comparison purposes, the *p* value for the seven-category CMH analysis was 0.0905.
§Pretreatment Mini-Mental State Examination (MMSE) values were taken at screening; *p* values for the MMSE were obtained from an ANCOVA with screening included as a covariate in the model change = treatment + pooled site + screening by treatment.
¶*p* Values for the Alzheimer Disease Cooperative Study–Activities of Daily Living–severe version (ADCS-ADL-sev) were obtained from an ANCOVA model with baseline included as a covariate in the model change = treatment + pooled site.
‖*p* Values for the Neuropsychiatric Inventory (NPI) were obtained from an ANCOVA model with baseline included as a covariate in the model change = treatment + pooled site.
ITT = intent-to-treat; LS = least squares; OC = observed case; LOCF = last observation carried forward.

status, cognition, function, and behavior showed that more donepezil patients improved or remained unchanged in comparison with the general worsening of the placebo patients. Although the CIBIC-Plus is scored on a seven-category Likert scale, it has been documented that collapsing the categories into three simpler groups of improved, no change, or worsened is more reliable as it resembles the global functioning that a clinician would typically evaluate in office practice. In the present study, the analysis using the collapsed categories revealed that clinicians rated improvement or no change in 66.1% of donepezil patients and 51.9% of placebo patients. Because the CIBIC-Plus is administered by an independent clinician with no access to the patient's test scores, these data help to confirm the clinical significance of the changes seen on other efficacy measures such as the SIB.

Small improvements from the screening score were seen on the MMSE in the donepezil group (change from screening score of +0.65), whereas the value for the placebo group was virtually unchanged from screening (change from screening score of −0.03). Nevertheless, the difference between the two groups was significant. Although it is commonly administered in the clinical setting to evaluate cognitive performance, care needs to be taken in using the MMSE to evaluate patients with severe disease because of floor effects as il-

Table 4 Adverse events (AEs) reported by ≥5% of patients in the donepezil group and considered possibly or probably related to treatment by the investigator

	Treatment group, n (%)	
AE	Donepezil (n = 176)	Placebo (n = 167)
Any AE	140 (79.5)	117 (70.1)
Any related AE*	74 (42.0)	51 (30.5)
Diarrhea	18 (10.2)	7 (4.2)
Anorexia	12 (6.8)	7 (4.2)
Nausea	12 (6.8)	3 (1.8)
Agitation	11 (6.3)	10 (6.0)
Vomiting	11 (6.3)	4 (2.4)

*Possibly or probably related.

lustrated by the lack of further decline in the placebo group.

On the ADCS-ADL-sev, baseline mean scores in both groups were approximately 27, or half of the total possible score, which is consistent with the severity of the subjects' impairment. Both groups declined about two points in the LOCF analysis (−1.82 [6.6%] for donepezil; −2.53 [9.5%] for placebo) and the treatment difference was not significant at endpoint. This pattern was similar to that observed in a previous study of donepezil for severe AD,[7] except that in that study the placebo group declined by more than 20% making the treatment difference significant. There are at least two possible explanations for the greater placebo decline in the previous study.[7] The first is that the baseline ADCS-ADL-sev score for both groups was about 14, indicating even more impairment than patients in the present study; this is consistent with the nursing home population in the previous study. The second relates to the fact that the ADL instruments used in AD clinical trials are all caregiver-reported and not based on patient performance. Professional caregivers in a nursing home setting may be more willing or more prone to acknowledge a decline than family caregivers in a community setting, although this would not seem to be the case in the memantine monotherapy study in community-based patients where the placebo group declined 19.0% vs 11.6% for the memantine group, and this difference was significant.[22]

Behavioral disturbances are another concern in this population because they often tip the balance toward nursing home placement. The patients in the present study had substantial behavioral symptoms, with baseline NPI scores of approximately 22 for both groups. As in a previous study of patients with severe AD,[7] both groups improved, so there was no significant difference between donepezil and placebo. Unlike the previous study, however, in the present study the placebo improvement was greater than donepezil and approached significance in the OC analysis. Confounding factors such as concomitant psychotropic medications may explain this somewhat surprising result. For prior psychotropic medications present at baseline and psychotropic medications started during the study, there were no differences between groups that were greater than 10%; however, where there were differences, they mostly reflected greater use for the placebo group. While these differences may explain some of the placebo response, manual examination of individual patient listings suggests that the explanation is more complex than this and further analysis will be required.

The remaining two efficacy measures, the CBQ and the RUSP, were included in an attempt to measure outcomes that would provide a more complete picture of the efficacy of donepezil in this patient population; they did not show changes from baseline or between groups. For the CBQ, it appears that this was because mean levels of stress due to caregiving were low—less than the value expected for mild AD; the mean hours spent assisting with ADLs were also relatively low—less than 6 hours. Both of these values were unexpected, and it is not clear whether there was a problem with the instrument itself, with the way it was administered, with the way it was analyzed, or whether the explanation is related to the caregivers and patients in the severe stage of AD who are still able to be managed in the community. Likewise for the RUSP, there was a low frequency of events such as permanent change in residence, emergency department visits, and hospitalizations, and low utilization of services such as Visiting Nurse, Meals on Wheels, and day care. These results are less surprising given the 6-month duration of the study, and they may reflect the relative stability of patients at this stage of the disease who are still living in the community. Nonetheless, these data should be further evaluated for the same possible problems as discussed for the CBQ.

Donepezil was relatively well tolerated in this population of patients with severe AD. The most common AEs reported are consistent with the known cholinergic side effects of donepezil.[23] The results from the present study are consistent with those from other trials of donepezil treatment in the population with severe AD. In a study of nursing home patients with severe AD, 82% of the donepezil group and 76% of the placebo group reported AEs.[7]

These findings, taken together with those of prior studies,[6,7] provide evidence to support what more recent basic research has already suggested—that cholinergic therapy, in this case donepezil, can benefit patients with severe disease.[24,25] The effectiveness of donepezil in preserving cognitive and global function in patients with severe AD, as evidenced by this trial and others, is encouraging when considered together with the wealth of clinical trial data and 10 years of patient use supporting the efficacy of donepezil in earlier disease stages. In view of the consistent positive results of trials in mild, moderate, and now severe

patient populations, donepezil may be considered to be beneficial throughout the course of AD.

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Donepezil preserves cognition and global function in patients with severe Alzheimer disease

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