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Effectiveness and Tolerability of High-Dose (23 mg/d) Versus Standard-Dose (10 mg/d) Donepezil in Moderate to Severe Alzheimer's Disease: A 24-Week, Randomized, Double-Blind Study

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Abstract

Background—Currently approved Alzheimer's disease (AD) treatments have been reported to provide symptomatic benefit, without proven impact on clinical progression. We hypothesized that the loss of initial therapeutic benefit over time may be mitigated by higher doses of a cholinesterase inhibitor.

Objective—The aim of this study was to determine the effectiveness and tolerability of increasing donepezil from 10 to 23 mg/d in patients with moderate to severe AD.

Methods—This randomized, double-blind study was conducted at 219 sites in Asia, Europe, Australia, North America, South Africa, and South America from June 6, 2007, to March 27, 2009. Patients aged 45 to 90 years with probable AD, Mini-Mental State Examination score 0 to 20 (moderate to severe impairment), and who were receiving donepezil 10 mg once daily for ≥12 weeks before the start of the study were eligible. Patients (n = 1467) were randomly assigned to receive high-dose donepezil (23 mg once daily) or standard-dose donepezil (10 mg once daily) for 24 weeks. Coprimary effectiveness measures were changes in cognition and global functioning, as assessed using least squares mean changes from baseline (LSM [SE] Δ) scores (last observation carried forward) on the Severe Impairment Battery (SIB; cognition) and the Clinician's Interview-Based Impression of Change Plus Caregiver Input scale (CIBIC+; global function rating) overall change score (mean [SD]) at week 24. Treatment-emergent adverse events (TEAEs) were assessed using spontaneous patient/caregiver reporting and open-ended questioning; clinical laboratory testing (hematology, biochemistry, and urinalysis panels analyzed by a central laboratory); 12-lead ECG; and physical and neurologic examinations, including vital sign measurements.

Results—The effectiveness analyses included 1371 patients (mean age, 73.8 years; 62.8% female; 73.5% white; weight range, 34.0–138.7 kg). A total of 296 of 981 patients (30.2%) withdrew from the donepezil 23-mg/d group; 87 of 486 patients (17.9%) withdrew from the

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donepezil 10-mg/d group. At study end (week 24), the LSM (SE) Δ in SIB score was significantly greater with donepezil 23 mg/d than with donepezil 10 mg/d (+2.6 [0.58] vs +0.4 [0.66], respectively; difference, 2.2; $P < 0.001$). The between-treatment difference in CIBIC+ score was nonsignificant (4.23 [1.07] vs 4.29 [1.07]). In post hoc analysis, LSM Δ in SIB score and CIBIC+ treatment effect at end point were greater with donepezil 23 mg/d than 10 mg/d in patients with more advanced AD compared with less impaired patients (SIB, +1.6 [0.78] vs −1.5 [0.88], respectively [$P < 0.001$]; CIBIC+, 4.31 [1.09] vs 4.42 [1.10] [$P = 0.028$]). TEAEs were reported in 710 of 963 patients (73.7%) who received donepezil 23 mg/d and in 300 of 471 patients (63.7%) who received donepezil 10 mg/d. With donepezil 23 mg/d, mild, moderate, and severe TEAEs were reported in 297 (30.8%), 332 (34.5%), and 81 (8.4%) patients, respectively; with donepezil 10 mg/d, these proportions were 147 (31.2%), 119 (25.3%), and 34 (7.2%). The 3 most common severe AEs reported with the 23-mg/d dose were nausea (9 patients [0.9%] vs 1 [0.2%] with the 10-mg/d dose), dizziness (7 [0.7%] vs 1 [0.2%]), and vomiting (6 [0.6%] vs 0). The most commonly reported TEAEs considered probably related to treatment with the 23-mg/d dose were nausea (59 patients [6.1%] vs 9 [1.9%] with the 10-mg/d dose), vomiting (48 [5.0%] vs 4 [0.8%]), and diarrhea (31 [3.2%] vs 7 [1.5%]). Thirteen deaths were reported during the study or within 30 days of study discontinuation (23 mg/d, 8 patients [0.8%]; 10 mg/d, 5 patients [1.1%]); all were considered unrelated to the study medication.

Conclusions—In this study in patients with moderate to severe AD, donepezil 23 mg/d was associated with greater benefits in cognition compared with donepezil 10 mg/d. The between-treatment difference in global functioning was not significant in the overall population. Patients with more advanced AD appeared to benefit from donepezil 23 mg/d on the assessment of global functioning, but this observation requires additional studies for confirmation.

Keywords

Alzheimer’s disease; cognitive disorders; dementia; randomized controlled clinical trials

INTRODUCTION

As Alzheimer’s disease (AD) advances, cognitive and functional capacities become progressively impaired[1,2] and caregiver burden increases. Approved pharmaco-therapies for AD, such as donepezil hydrochloride[3]; other acetylcholinesterase inhibitors (AChEIs), such as rivastigmine and galantamine[4]; and memantine, an *N*-methyl-D-aspartate receptor antagonist,[5] have been reported to provide symptomatic benefits that are lost with disease progression over time despite continued treatment.[6–8] To sustain symptomatic cognitive and functional benefits, clinicians might prescribe combination therapy, such as donepezil plus memantine.[5,9,10] There are no other established evidence-based options in patients with disease progression.[2,7] Because clinical decline in AD has been associated with the deterioration of cholinergic neurons,[11,12] it is unclear whether patients with moderate to severe AD can benefit from higher doses of AChEIs.[13]

Donepezil hydrochloride is a selective, reversible AChEI believed to enhance central cholinergic function.[14] The current maximum daily dose (10 mg) approved by the US Food and Drug Administration (FDA), the UK Medicines and Healthcare Products Regulatory Agency, and other regulatory authorities is available in an immediate-release (IR) tablet formulation.[3] A matrix-type (sustained-release [SR]) tablet of 23 mg was developed to provide a higher once-daily dose while avoiding a sharp daily increase in peak concentration. The drug exposure with the SR formulation is ~92% (95% CI, 89.1–94.7; dose adjusted) that of the IR formulation, with a T_{max} that is <2-fold greater (6–9 hours with SR vs 3–4 hours with IR) and an $AUC_{0-\infty}$ that is >2-fold greater (data on file, Eisai Inc., study no. E2020-G000-326, 2009).

The currently approved doses of 5 and 10 mg/d of donepezil have been associated with 20% to 30% inhibition of cortical AChE activity.[15,16] In a study in 61 Japanese patients with AD who were receiving a stable dose of donepezil 5 mg/d, a dose increase to 10 mg/d for 24 weeks was associated with more effective prevention of deterioration in severe AD, as measured using the Revised Hasegawa Dementia Scale and Mini-Mental State Examination (MMSE).[17,18] Based on those findings, doses of AChEIs that are higher than those currently approved might provide greater stabilization and/or symptomatic improvement in later stages of AD. A finding that increasing cholinesterase inhibition confers further benefits in moderate to severe disease, including in patients receiving combination therapy, would have implications for extending and/or improving AD treatment and significant value for public health.[19]

The objective of this study was to compare the effectiveness and safety profile of high-dose donepezil (23 mg/d) and standard-dose donepezil (10 mg/d) in patients with moderate to severe AD.

PATIENTS AND METHODS

This randomized, double-blind study was conducted at 219 sites in Asia, Europe, Australia, North America, South Africa, and South America from June 6, 2007, to March 27, 2009. The protocol and informed-consent form were approved by the independent ethics committee/institutional review board for each independent research site and conformed to the principles of the World Medical Association Declaration of Helsinki and all local regulations. The study design was reviewed and deemed appropriate by the FDA and other regulatory agencies.

Study Population

Eligible patients were 45 to 90 years of age and had a diagnosis of probable dementia of the Alzheimer's type, as defined in the *Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition*[1] (code 290.00 or 290.10) and based on the National Institute of Neurological and Communicative Diseases and Stroke–Alzheimer's Disease and Related Disorders Association criteria[20]; had an MMSE score of 0 to 20 (moderate to severe impairment) and a Severe Impairment Battery (SIB)[21,22] score ≤90; had a Cornell Scale for Depression in Dementia[23] score <12; were otherwise physically healthy and ambulatory or ambulatory aided; and had clinical laboratory values within normal limits or, if abnormal, considered by the investigator to be clinically nonsignificant. Patients with the following comorbidities were considered eligible if the condition was deemed by the investigator to be stable and well controlled: hypertension (supine diastolic blood pressure <95 mm Hg); cardiovascular disease (stable on appropriate medication for ≥12 weeks before screening); diabetes mellitus (stable with no hospitalizations for diabetic ketoacidosis, hyperosmolar coma, or hypoglycemia within 12 weeks before screening); non–insulin-dependent diabetes (controlled with diet and/or oral medications); and hypothyroidism (controlled on a stable dose of medication for ≥12 weeks before screening, normal thyroid-stimulating hormone and free T4 concentrations at screening, and considered euthyroid). Eligible patients were also receiving a stable, single daily dose of donepezil 10 mg for ≥12 weeks before the start of the study. Donepezil use was confirmed by the presence of detectable plasma donepezil concentrations.

Patients were excluded if they had an additional neurologic disorder that might, in the investigator's opinion, affect cognition or the assessment of cognition, even if the disorder was distinguishable from AD (including Parkinson's disease, multi-infarct dementia, dementia due to cerebrovascular disease, Huntington's disease, frontotemporal dementia, Creutzfeldt-Jakob disease, Lewy body dementia, normal-pressure hydrocephalus, brain

tumor, progressive supranuclear palsy, seizure disorder, subdural hematoma, or multiple sclerosis). Magnetic resonance imaging or computed tomography within a year before screening was used to rule out causes of dementia other than probable AD.

Before conducting study procedures, investigators obtained written informed consent from each patient, if possible, or from the patient's legal guardian or representative. If a patient was unable to provide written consent, he or she was required to provide verbal assent to participate in the study, with documentation of assent noted in the study record, and a caregiver was required to separately provide written informed consent for his/her own participation in the study. Caregivers were required to be sufficiently familiar with the patient to provide data on global functioning, with regular contact ≥10 hours/week, and could not be clinically depressed (>15 on the Center for Epidemiologic Studies–Depression scale)[24] or cognitively impaired (MMSE <27 or <25 if illiterate).

Study Drug Administration

Patients were randomly assigned, in a 2:1 ratio using computer-generated randomization codes, to receive donepezil 23 mg (test) or donepezil 10 mg (reference) once daily for 24 weeks. Patients, caregivers, and study personnel were blinded to treatment assignment. Block size was 6, with site as the unit. Stratification was based on whether a patient was concurrently taking memantine at baseline. If a patient was taking memantine at a stable dose of ≤20 mg/d for ≥12 weeks before screening, use was allowed to continue. All additional prescriptions for AD, including other cholinesterase inhibitors, were required to have been discontinued for ≥12 weeks before screening. Atypical antipsychotics and selective serotonin reuptake inhibitors were permitted, the latter provided that doses were less than or equal to the approved range for therapeutic effectiveness as specified in the *Physicians' Desk Reference*[25] or regional equivalent, and that the dose was stable for ≥12 weeks before screening. The use of any medication known to interfere with the clinical effects of donepezil (eg, anticholinergics such as oxybutynin) or that could substantially impact cognition, either by enhancing alertness or causing sedation, was not permitted.

Because the treatments were not identical in appearance, a double-dummy design was used to maintain blinding. Study medication was provided free of charge and was administered at any time of day, provided that the time was consistent.

To determine compliance, unused tablets were counted and recorded by a designated staff member at the study site at each clinic visit (weeks 6, 12, 18, and 24), with the number of days since the last visit recorded as the treatment period. The number of tablets remaining was subtracted from the number of tablets dispensed; this value was divided by the number of days in the treatment period.

Effectiveness and Tolerability Assessments

Patients were asked to return to the clinic for effectiveness and tolerability assessments at treatment weeks 3 (tolerability only), 6, 12, 18, and 24. The coprimary effectiveness measures were changes in cognition and global functioning, as assessed using the SIB (cognition) and the Clinician's Interview-Based Impression of Change Plus Caregiver Input scale (CIBIC+; global function rating). The SIB is a 40-item instrument administered to the patient that assesses cognitive function in patients with more advanced dementia.[21,22] Total scores range from 0 (most impaired) to 100 (least impaired). The CIBIC+ is a semistructured tool administered by an independent clinician interviewing the patient and caregiver that assesses overall change and change in various domains of patient functioning[26,27] on a 7-point scale (1 = marked improvement; 2 = moderate improvement; 3 = minimal improvement; 4 = no change; 5 = minimal worsening; 6 = moderate worsening; and 7 =

marked worsening). The CIBIC+ rating uses baseline disease severity as a point of reference, captured by the Clinician's Interview-Based Impression of Severity Plus Caregiver Input scale (CIBIS+).

Secondary effectiveness variables were scores on the Alzheimer's Disease Cooperative Study–Activities of Daily Living scale (severe version) (ADCS-ADL)[28] and the MMSE. The ADCS-ADL is a 19-item instrument with total scores ranging from 0 (most impaired) to 54 (least impaired). The MMSE is a 30-item test of cognitive function, with total scores ranging from 0 (most impaired) to 30 (least impaired).[17]

All of the effectiveness assessments were conducted by systematically trained site raters after meeting qualification standards, including education and years of experience with the patient population.

Tolerability assessments included clinical laboratory testing (hematology, biochemistry, and urinalysis panels analyzed by a central laboratory that met regulatory certification requirements), 12-lead ECG read by a cardiologist or physician with advanced training, and physical and neurologic examinations, including vital sign measurements, at all clinic visits. Blood pressure was measured in triplicate after ≥5 minutes in the supine position; after ≥2 minutes in the standing position, blood pressure measurements were repeated. Heart rate was determined in the supine and standing positions at all clinic visits using the radial pulse, auscultation over the heart with a stethoscope, or other accepted means. Temperature, respiratory rate, and weight were also determined at all clinic visits. Height was recorded only at screening. Treatment-emergent adverse events (TEAEs) were recorded throughout the study and were determined using spontaneous reports from patients and/or caregivers and open-ended questioning. The investigators determined the severity of each TEAE (mild, moderate, or severe) and its relationship to the study treatment (unrelated, possibly related, or probably related).

Statistical Analysis

Sample size was calculated based on the findings from the randomized, placebo-controlled, parallel-group study by Tariot et al,[5] in which memantine 20 mg/d or placebo was added to an existing regimen of donepezil 5 to 10 mg/d in 404 patients with probable AD, with meaningful treatment differences found. In the current study, ~1200 patients (donepezil 23 mg/d, 800; donepezil 10 mg/d, 400) were planned to be enrolled in the study to provide an overall power of ≥80% to find a significant difference between treatment groups (least squares mean change from baseline [LSM Δ], 3.0 on the SIB; 0.20 at week 24 on the CIBIC +). To assess whether the higher dose was associated with new or substantially increased safety concerns compared with the 10-mg dose, an interim tolerability analysis was conducted without statistical testing after the first 400 subjects in the intent-to-treat (ITT) population (patients who received ≥1 dose of study medication and in whom either [1] the SIB total score was available at baseline and ≥1 SIB total score was available after the administration of the first dose of study medication or [2] the CIBIS+ score was available at baseline and ≥1 CIBIC+ overall change score was available after the administration of the first dose of study medication) had completed or discontinued from the study. An independent safety monitoring board determined that the study could proceed as planned. All statistical tests were conducted using SAS version 8.0 or higher (SAS Institute Inc., Cary, North Carolina) and were 2-sided at a significance level of 0.05.[29]

Effectiveness was analyzed in the ITT population. Tolerability was analyzed in the safety population (all randomized patients who received ≥1 dose of study medication and who had data available from ≥1 post-baseline tolerability assessment).

An ANCOVA model with terms for baseline score, country, and treatment was used as the primary model for testing treatment effects on SIB score, with LSM (SE) Δ used to compare treatment groups. Similar analyses were conducted for the ADCS-ADL and MMSE. For the categoric end point, CIBIC+ score at week 24, a nonparametric ANCOVA method combined with a Cochran-Mantel-Haenszel test component was used.[30] The analysis was adjusted for baseline CIBIS+ score, with a stratification adjustment for country. Additional prespecified analyses were based on whether patients were receiving memantine concurrently at baseline.

To further examine the coprimary end points, post hoc sensitivity analyses of the impact of baseline disease severity on treatment response were conducted in patients with baseline MMSE scores from 0 to 16 (more severe impairment) versus 17 to 20 (less severe impairment) and in the subgroup of patients from the United States (the country that randomized the largest number of patients [31.7% vs ≤8.0% from any other country]), which allowed a meaningful post hoc analysis of a sizable subpopulation (n = 432) with a more uniform basis of health care and clinical practice. A similar approach has been used by others.[31]

The primary effectiveness analyses used the last-observation-carried-forward (LOCF) method to impute missing values. The observed-cases (OC) population (patients who provided data at a given visit) at week 24 was also assessed to support the findings from the coprimary analyses.

RESULTS

Patient Disposition and Baseline Characteristics

Patient disposition is presented in Figure 1. Site and patient distributions by country are shown in Table I. The baseline demographic and clinical characteristics of the safety population are presented in Table II (donepezil 23 mg/d, n = 963; donepezil 10 mg/d, n = 471; female, 63.0% and 62.4%, respectively). All baseline characteristics were comparable between the 2 treatment groups. Concurrent use of medication classes appeared proportionally similar between the 2 treatment groups. The medication classes most frequently concurrently used during the study were psychoactive agents (memantine and antidepressants, 50.3%), lipid-lowering agents (32.6%), and antithrombotic agents (31.9%). Memantine was prescribed concurrently in 36.6% and 35.7% of patients in the 23- and 10-mg/d groups, respectively; antidepressants in 25.1% and 26.3%; and antipsychotics in 11.1% and 10.0%. The mean durations of prior treatment with donepezil were 112.17 and 104.76 weeks.

Baseline disease severity as assessed using the MMSE and SIB was not notably different between the 2 treatment groups. Patients with more severe impairment (baseline MMSE 0–16) and US patients had lower mean SIB and poorer CIBIS+ scores at baseline, longer prior treatment with donepezil, and higher rates of concomitant memantine use than did the overall ITT population.

Treatment compliance rates were 93.2% in the high-dose group and 97.3% in the standard-dose group.

Effectiveness

SIB—At study end (week 24), the LSM (SE) Δ in SIB score (ITT-LOCF) was significantly greater with donepezil 23 mg/d than with donepezil 10 mg/d (+2.6 [0.58] vs +0.4 [0.66], respectively; difference, 2.2; $P < 0.001$). Similar results were found in the OC population,

with a 2.4-point LSM difference between the 2 treatment groups ($P < 0.001$) (Figure 2 and Table III).

In the OC population, the LSM Δ was significantly greater with donepezil 23 mg/d at weeks 6 ($P < 0.05$), 12 ($P < 0.001$), 18 ($P < 0.01$), and 24 ($P < 0.001$) (Figure 2). In both subgroups of patients concurrently taking and not taking memantine, the LSM Δ was significantly greater with donepezil 23 mg/d ($P = 0.003$ and $P = 0.007$, respectively, vs 10 mg) (Table III).

CIBIC+—In the ITT population, mean (SD) CIBIC+ scores at week 24 (LOCF) were 4.23 (1.07) with donepezil 23 mg/d and 4.29 (1.07) with donepezil 10 mg/d; the difference was not statistically significant. In the CIBIC+ OC population analysis, global scores were 4.18 (1.11) with 23 mg/d versus 4.28 (1.09) with 10 mg/d (P = NS). In the subgroups of patients receiving and not receiving concurrent memantine, CIBIC+ overall change scores were not statistically significantly different between treatment groups (Table III).

Secondary End Points—No incremental benefit of high-dose donepezil was found in ADCS-ADL or MMSE total scores in the ITT population. There was little change from baseline on the ADCS-ADL scale at study end (LSM Δ, −1.2 in both groups). The MMSE score was numerically increased compared with baseline (LSM, +0.4 and +0.2 with 23 and 10 mg/d, respectively) (Figure 2), with no statistically significant incremental benefit with the 23-mg/d dose (Table III).

Impact of AD Severity on Treatment Response—In the post hoc analysis of the impact of baseline disease severity on treatment response based on the positive SIB results in the overall study population (Table III), greater treatment effects were found in patients with more impairment at baseline (MMSE score 0–16), representing >70% of the study population. In these patients, the between-treatment differences in LSM Δ in SIB score were 3.1 (ITT, $P < 0.001$) and 3.4 (OC, $P < 0.001$), which were numerically greater than the treatment differences in the overall population (2.2 and 2.4, respectively). In patients with more impairment at baseline, those in the 23-mg/d group showed improvement compared with baseline (+1.6), whereas in patients continuing on the 10-mg dose, the score declined (−1.5). Treatment differences in SIB scores were not found in patients with less impairment at baseline (MMSE score 17–20) (Table III). Significantly greater treatment differences in LSM Δ SIB scores were found in the sub-population of US patients (more impaired at the start of the study compared with the overall population) (ITT, 3.9 [$P < 0.001$]; OC, 4.1 [$P = 0.001$]).

Similarly, on the global functioning measure, the between-treatment difference in CIBIC+ overall change score at week 24 was not significant in the overall patient population, but was significant in patients with more impairment at baseline (MMSE score 0–16) ($P = 0.028$) and in the US patients ($P = 0.033$) (Table III).

Tolerability

TEAEs occurring in ≥2% of patients in the 23-mg/d group that were also reported at a higher frequency than in the 10-mg/d treatment group are presented in Table IV. Overall, 710 of 963 patients (73.7%) who received the 23-mg/d dose and 300 of 471 (63.7%) in the 10-mg/d group experienced ≥1 AE during the study. In both treatment groups, gastrointestinal (GI) TEAEs occurred at the highest frequency within the first month after starting study medication (23 mg/d, 21.0% of patients reporting first onset of any GI TEAE in the first month, ~3% thereafter; 10 mg/d, 5.9% and ~2% thereafter). In both treatment groups, most patients reported TEAEs that were mild or moderate in severity (23 mg/d, 297

[30.8%] mild, 332 [34.5%] moderate, and 81 [8.4%] severe; 10 mg/d, 147 [31.2%] mild, 119 [25.3%] moderate, and 34 [7.2%] severe). More patients in the 23-mg/d dose group had TEAEs that were classified by the investigators as possibly or probably related to treatment (301 [31.3%] and 173 [18.0%], respectively) compared with the 10-mg/d dose group (97 [20.6%] and 33 [7.0%]). The 3 most common severe AEs reported with the 23-mg/d dose were nausea (9 patients [0.9%] vs 1 [0.2%] with the 10-mg/d dose), dizziness (7 [0.7%] vs 1 [0.2%]), and vomiting (6 [0.6%] vs 0). The most commonly reported TEAEs considered probably related to treatment with the 23-mg/d dose were nausea (59 patients [6.1%] vs 9 [1.9%] with the 10-mg/d dose), vomiting (48 [5.0%] vs 4 [0.8%]), and diarrhea (31 [3.2%] vs 7 [1.5%]). There were no notable findings or clinically meaningful differences between treatment groups in clinical laboratory assessments, vital signs, or ECGs. Although no notable changes in mean weight were observed in either treatment group, decreased weight as an AE was reported in 45 patients (4.7%) in the 23-mg/d group and 12 patients (2.5%) in the 10-mg/d group. Compared with baseline weight, 11.3% of patients in the donepezil 23-mg group had a weight decrease of ≥7% at any time during the study (79 [8.4%] at the end of the study) compared with 7.4% at any time in the group who received 10 mg (23 [4.9%] at the end of the study). Patients in the 23-mg/d treatment group with lower weight at baseline (<55 kg) had a higher incidence of TEAEs (178/218 [81.7%]) than did patients with higher weight (531/744 [71.4%]).

Thirteen patients died during the study or within 30 days after the administration of the last dose (8 [0.8%] in the 23-mg/d group and 5 [1.1%] in the 10-mg/d group); none of the deaths were considered related to the study medication. Serious TEAEs occurred in 80 patients (8.3%) in the 23-mg/d group and 45 patients (9.6%) in the 10-mg/d group (Table V); the majority (53/80 [66.3%] in the 23-mg/d group and 34/45 [75.6%] in the 10-mg/d group) were considered not related to treatment. More patients in the 23-mg/d group (182 [18.6%]) discontinued due to TEAEs than patients in the 10-mg/d group (39 [7.9%]); of the total discontinuations due to AEs in the higher-dose group, the majority of those discontinuations occurred during the first month of treatment (108 patients [60.3%]). The most common (occurring in ≥1% in either group) TEAEs that led to discontinuation in the 23- and 10-mg/d groups were vomiting (28 [2.9%] and 2 [0.4%], respectively), nausea (18 [1.9%] and 2 [0.4%]), diarrhea (16 [1.7%] and 2 [0.4%]), and dizziness (11 [1.1%] and 0).

DISCUSSION

In this large-scale, randomized, double-blind study in patients with moderate to severe AD who were already receiving 10 mg/d of donepezil IR, statistically significant benefit on 1 of the 2 prespecified coprimary outcome measures was found with donepezil 23 mg/d compared with continued 10-mg/d treatment. Although benefit was found in cognition as measured on the SIB, no incremental benefit above that achieved with 10-mg/d treatment was found on global functioning as measured using the CIBIC+.

This study assessed whether patients with moderate to severe dementia, who are presumed to have greater loss of brain cholinergic function and therefore reduced acetylcholine production, would respond to higher doses of a cholinesterase inhibitor. The data support the idea that patients with more advanced AD can still achieve therapeutic benefit. The post hoc analyses found greater treatment effect on the SIB when the less impaired patients were excluded from the analysis. Although these analyses were post hoc, they are also consistent with significant benefit of donepezil 23 mg/d on the CIBIC+ in more advanced patients. The magnitude of change on the SIB found in the more impaired patients was similar to that observed when memantine was added to a regimen of donepezil in the study by Tariot et al.[5] The findings from that trial were used to support the approval of combination therapy with donepezil and memantine, which is now used in clinical practice.

From the standpoint of clinical use, it is expected that a higher dose of donepezil would be tried when lower doses had already been used and either did not achieve the expected effect, or after initial treatment benefit was either clinically insufficient or appeared to wane. This study was therefore designed to compare the effects of a dose increase to 23 mg/d with those of continued treatment with 10 mg/d of donepezil. Because continued treatment in practice would likely be based on tolerability, it is of interest to examine the results in those patients who were able to complete the entire 24 weeks of study treatment. In this OC population (n = 1084), the difference between treatments on the SIB and the effect of 23 mg/d on the CIBIC+ were more robust than in the ITT population. In addition, clinicians commonly prescribe memantine for an additive benefit in patients with moderate to severe AD who are already receiving donepezil 10 mg/d. Benefits on cognition were found in this study regardless of whether patients were receiving memantine concurrently. Data from the US patient population, ~32% of the total safety population, also support the view that donepezil 23 mg/d benefited patients with more advanced AD: US patients were somewhat more impaired at baseline and were more likely to be receiving memantine than was the overall patient population. In those patients, there was a treatment difference favoring the higher dose on both coprimary measures.

There was no significant incremental benefit with the 23-mg/d dose above that with the 10-mg/d dose on the secondary end points, ADCS-ADL and MMSE. The ADCS-ADL scale has shown good sensitivity to changes in function in response to treatment compared with placebo.[33] However, there are limitations for this class of instruments,[34] and some previous studies report no difference in ADCS-ADL even when the active drug showed significant cognitive advantage.[35,36] In addition, the ADCS-ADL scale may not be sufficiently applicable in global studies; variability in cultural differences in activities of daily living, caregiving practices, or disease stage severity of the patient population being assessed may have limited the ability to measure change despite common training across all raters who conducted the assessments, which was aimed at harmonizing assessment methodology. In a previously published study in patients with severe AD who were receiving donepezil,[8] little change occurred on the ADCS-ADL scale in the 10-mg/d treatment group over 24 weeks (−1.4 points from baseline). Similarly, patients in the current study had little change in ADCS-ADL during the study (−1.2 points in 24 weeks). That there was little change on the MMSE may be due in part to the fact that the patient population had moderate to severe AD, as the scale is known to exhibit floor effects and thus there would be little opportunity for change in patients with lower MMSE scores.[37]

When donepezil is titrated from 5 to 10 mg/d, there is an increase in AEs.[3,38] The current study design involved increasing the dose to 23 mg/d from background treatment with 10 mg/d donepezil in patients who tolerated the latter dose. Thus, the observed pattern of AEs was expected. Overall, the TEAEs of nausea, vomiting, and diarrhea were the most common treatment-related events in the 23-mg/d group and also occurred more frequently than in the 10-mg/d group and in association with the dose escalation. Patients of lower initial weight (<55 kg) experienced more TEAEs than did those weighing more. The discontinuation rate due to TEAEs was numerically higher in the 23-mg/d group, mostly reflecting a higher rate of GI-related TEAEs. There were no dose-related increases in serious TEAEs, deaths, or TEAEs associated with institutionalization, such as agitation and falls.

Because of the global nature of this trial, the ability to detect treatment differences may have been confounded by different interpretations of the assessment scales and variations in the patient population with respect to baseline disease severity or duration of prior donepezil exposure, because these varied considerably in the different regions. The trial design also did not permit an assessment of the interaction between the effects of the higher donepezil dose and concurrent use of memantine, because patients were enrolled regardless of

concurrent memantine use, and at baseline, patients who were concurrently receiving memantine had more severe AD compared with those who were not. The analyses based on disease severity and region were not prespecified (post hoc). In addition, the methodology for compliance assessment, while standard, cannot be used to assess actual medication intake.

Future research should further examine the suggestion that patients with more cognitive impairment are the most appropriate population for higher donepezil doses and the long-term outcome of such treatment.

CONCLUSIONS

In this study in patients with moderate to severe AD who were receiving a stable dose of donepezil 10 mg/d, donepezil 23 mg/d provided significantly greater cognitive benefit as measured using the SIB. Although no significantly greater effect on global functioning as measured by CIBIC+ was found with the dose increase in the overall population, findings from the post hoc analyses of the SIB suggested that more severely impaired patients may also experience a global benefit (CIBIC+) with an increase to the higher donepezil dose.

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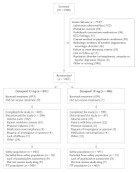

Figure 1.
Patient disposition in this study of the effectiveness and tolerability of donepezil 23 or 10 mg/d in patients with moderate to severe Alzheimer's disease. ITT = intent-to-treat (patients who received ≥1 dose of study medication and in whom either [1] the Severe Impairment Battery [SIB][21,22] total score was available at baseline and ≥1 SIB total score was available after the administration of the first dose of study medication or [2] the Clinician's Interview-Based Impression of Severity Plus Caregiver Input scale [CIBIS+] score was available at baseline and ≥1 Clinician's Interview-Based Impression of Change Plus Caregiver Input scale [CIBIC+][26,27] overall change score was available after the administration of the first dose of study medication). *If a patient failed screening for multiple reasons, he or she was counted under each reason.

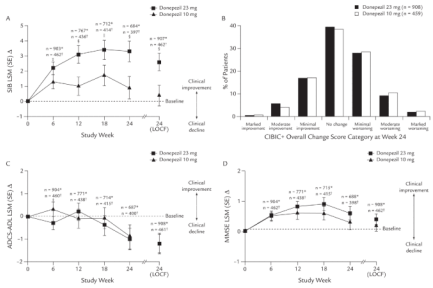

Figure 2.
Effectiveness of donepezil 23 or 10 mg/d in patients with moderate to severe Alzheimer's disease. (A) Changes from baseline in Severe Impairment Battery (SIB)[21,22] total score (observed cases [OC] and intent-to-treat [ITT], last observation carried forward [LOCF]). (B) Frequency distribution of Clinician's Interview-Based Impression of Change Plus Caregiver Input (CIBIC+)[26,27] scores at week 24 (ITT-LOCF). (C) Changes from baseline in Alzheimer's Disease Cooperative Study–Activities of Daily Living (ADCS-ADL)[28] total score (OC and ITT-LOCF). (D) Changes from baseline in Mini-Mental State Examination (MMSE)[17] total score (OC and ITT-LOCF). LSM = least squares mean. *Donepezil 23 mg; †donepezil 10 mg; ‡$P < 0.05$ between treatment groups; §$P < 0.001$ between treatment groups; and ‖$P < 0.01$ between treatment groups.

Table I

Global enrollment statistics in this study of the effectiveness and tolerability of donepezil 23 or 10 mg/d in patients with moderate to severe Alzheimer's disease.

Country	No. of Sites (n = 209)	No. of Randomized Patients (n = 1467)
United States	61	465
India	18	113
Poland	14	86
Germany	12	76
South Africa	10	77
South Korea	9	92
Spain	9	62
Chile	5	77
Argentina	5	67
Other*	66	352

*Countries with <50 randomized patients (sites/patients): Australia (10/37); Italy (8/31); France (8/26); Israel (7/44); United Kingdom (6/32); Austria (5/35); Lithuania (4/36); Croatia (4/35); Romania (4/19); Taiwan (3/31); Hong Kong (2/15); Sweden (2/7); Singapore (2/2); and Denmark (1/2).

Table II

Baseline demographic and clinical characteristics of the safety population in this study of the effectiveness and tolerability of donepezil 23 or 10 mg/d in patients with moderate to severe Alzheimer's disease.*†

	Patients With Baseline MMSE Score 0–16		US Patients		All Patients	
Characteristic	**Donepezil 23 mg/d (n = 676)**	**Donepezil 10 mg/d (n = 338)**	**Donepezil 23 mg/d (n = 308)**	**Donepezil 10 mg/d (n = 146)**	**Donepezil 23 mg/d (n = 963)**	**Donepezil 10 mg/d (n = 471)**
Age, mean (SD), y	73.4 (8.65)	73.4 (8.74)	74.5 (8.74)	75.0 (8.20)	73.9 (8.53)	73.8 (8.56)
Sex, no. (%)						
Female	437 (64.6)	224 (66.3)	194 (63.0)	94 (64.4)	607 (63.0)	294 (62.4)
Male	239 (35.4)	114 (33.7)	114 (37.0)	52 (35.6)	356 (37.0)	177 (37.6)
Race, no. (%)						
White	489 (72.3)	234 (69.2)	268 (87.0)	129 (88.4)	708 (73.5)	346 (73.5)
Asian/Pacific Islander	117 (17.3)	68 (20.1)	0	1 (0.7)	161 (16.7)	87 (18.5)
Hispanic	47 (7.0)	24 (7.1)	18 (5.8)	7 (4.8)	67 (7.0)	26 (5.5)
Black	19 (2.8)	9 (2.7)	22 (7.1)	9 (6.2)	22 (2.3)	9 (1.9)
Other	4 (0.6)	3 (0.9)	0	0	5 (0.5)	3 (0.6)
Weight						
Group, no. (%)						
<55 kg	162 (24.0)	88 (26.0)	43 (14.0)	26 (17.8)	218 (22.6)	111 (23.6)
55–<65 kg	176 (26.0)	94 (27.8)	60 (19.5)	34 (23.3)	245 (25.4)	129 (27.4)
65–<75 kg	162 (24.0)	73 (21.6)	94 (30.5)	32 (21.9)	240 (24.9)	110 (23.4)
≥75 kg	175 (25.9)	83 (24.6)	111 (36.0)	54 (37.0)	259 (26.9)	121 (25.7)
Data unavailable	1 (0.1)	0	0	0	1 (0.1)	0
Range, kg	34.0–129.3	35.0–111.6	37.7–138.7	43.2–111.6	34.0–138.7	35.0–112.0
Living arrangements, no. (%)						
Lives with caregiver	561 (83.0)	269 (79.6)	249 (80.8)	107 (73.3)	780 (81.0)	365 (77.5)
Lives with relative or friend	67 (9.9)	27 (8.0)	26 (8.4)	12 (8.2)	97 (10.1)	45 (9.6)
Lives alone	17 (2.5)	18 (5.3)	13 (4.2)	8 (5.5)	34 (3.5)	30 (6.4)
Residence, no. (%)						
Assisted-living facility	14 (2.1)	16 (4.7)	13 (4.2)	17 (11.6)	20 (2.1)	20 (4.2)
Senior residence or retirement home	6 (0.9)	4 (1.2)	3 (1.0)	2 (1.4)	14 (1.5)	5 (1.1)
Skilled nursing care facility	5 (0.7)	1 (0.3)	3 (1.0)	0	7 (0.7)	2 (0.4)

Characteristic	Patients With Baseline MMSE Score 0–16		US Patients		All Patients	
	Donepezil 23 mg/d (n = 676)	Donepezil 10 mg/d (n = 338)	Donepezil 23 mg/d (n = 308)	Donepezil 10 mg/d (n = 146)	Donepezil 23 mg/d (n = 963)	Donepezil 10 mg/d (n = 471)
Intermediate nursing care facility	2 (0.3)	0	0	0	3 (0.3)	0
Other	4 (0.6)	3 (0.9)	1 (0.3)	0	8 (0.8)	4 (0.8)
Duration of prestudy donepezil 10 mg/d treatment, mean (SD), wk	122.01 (114.97)	109.84 (106.15)	167.52 (120.69)	166.67 (117.96)	112.17 (108.18)	104.76 (98.98)
Concurrent memantine use, no. (%)	272 (40.2)	137 (40.5)	231 (75.0)	108 (74.0)	352 (36.6)	168 (35.7)
CIBIS+ score group, no. (%)						
Borderline mentally ill	1 (0.1)	1 (0.3)	1 (0.3)	0	7 (0.7)	5 (1.1)
Mildly mentally ill	30 (4.4)	27 (8.0)	30 (9.7)	13 (8.9)	99 (10.3)	55 (11.7)
Moderately mentally ill	266 (39.3)	136 (40.2)	136 (44.2)	69 (47.3)	451 (46.8)	217 (46.1)
Markedly mentally ill	275 (40.7)	120 (35.5)	98 (31.8)	46 (31.5)	300 (31.2)	138 (29.3)
Severely mentally ill	96 (14.3)	52 (15.4)	38 (12.3)	17 (11.6)	97 (10.1)	53 (11.3)
Among the most extremely mentally ill	4 (0.6)	2 (0.6)	4 (1.3)	1 (0.7)	4 (0.4)	2 (0.4)
Data unavailable	4 (0.6)	0	1 (0.3)	0	5 (0.5)	1 (0.2)

MMSE = Mini-Mental State Examination[17]; CIBIS+ = Clinician's Interview-Based Impression of Severity Plus Caregiver Input scale.

*The final total patient number was higher than planned due to an unexpected surge in enrollment during the final weeks of the recruitment period.

†Percentages may not total 100 due to rounding.

Table III

Effectiveness of 24-week treatment with donepezil 23 or 10 mg/d in patients with moderate to severe Alzheimer's disease (AD).

	Baseline, ITT Population,[a] Mean (SD)		24 Weeks, ITT Population, LSM (SE) Δ (LOCF)			24 Weeks, OC Population,[b] LSM (SE) Δ		
Parameter	**Donepezil 23 mg/d**	**Donepezil 10 mg/d**	**Donepezil 23 mg/d**	**Donepezil 10 mg/d**	***P***	**Donepezil 23 mg/d**	**Donepezil 10 mg/d**	***P***
SIB[c]								
All patients[d]								
n	907	462	907	462	–	684	397	–
Value	74.2 (17.58)	75.6 (16.28)	+2.6 (0.58)	+0.4 (0.66)	<0.001	+3.3 (0.69)	+0.9 (0.75)	<0.001
Concurrent memantine[e]								
Yes								
n	338	163	338	163	–	246	139	–
Value	72.0 (20.13)	74.7 (17.68)	−0.2 (1.27)	−3.0 (1.36)	0.003	+0.9 (1.20)	−2.3 (1.35)	0.003
No								
n	569	299	569	299	–	438	258	–
Value	75.4 (15.75)	76.1 (15.47)	+3.1 (0.61)	+1.3 (0.72)	0.007	+3.6 (0.71)	+1.7 (0.79)	0.008
Baseline AD severity[f]								
More advanced (baseline MMSE 0–16)								
n	641	331	641	331	–	490	285	–
Value	70.1 (19.03)	72.3 (17.75)	+1.6 (0.78)	−1.5 (0.88)	<0.001	+2.1 (0.80)	−1.3 (0.91)	<0.001
Less impairment (baseline MMSE 17–20)								
n	265	131	265	131	–	265	131	–
Value	83.8 (6.96)	84.0 (6.31)	+4.3 (0.54)	+4.3 (0.63)	0.939	+5.0 (0.62)	+4.8 (0.69)	0.764
US Population[f]								
n	292	141	292	141	–	211	123	–
Value	73.1 (10.31)	76.6 (15.43)	+2.7 (0.59)	−1.2 (0.85)	<0.001	+3.0 (0.72)	−1.1 (0.95)	0.001
CIBIS+/CIBIC+[g]								
All patients[h]								
n	904	461	908	459	–	682	395	
Value	4.42 (0.85)	4.38 (0.89)	4.23 (1.07)	4.29 (1.07)	0.179	4.18 (1.11)	4.28 (1.09)	0.059
Concomitant memantine[e]								

	Baseline, ITT Population,[a] Mean (SD)		24 Weeks, ITT Population, LSM (SE) Δ (LOCF)			24 Weeks, OC Population,[b] LSM (SE) Δ		
Parameter	**Donepezil 23 mg/d**	**Donepezil 10 mg/d**	**Donepezil 23 mg/d**	**Donepezil 10 mg/d**	***P***	**Donepezil 23 mg/d**	**Donepezil 10 mg/d**	***P***
Yes								
n	336	163	338	161		245	136	
Value	4.58 (0.88)	4.60 (0.84)	4.40 (1.02)	4.52 (0.94)	0.137	4.38 (1.05)	4.54 (0.97)	0.107
No								
n	568	298	570	298		437	259	
Value	4.32 (0.82)	4.26 (0.89)	4.12 (1.09)	4.16 (1.12)	0.380	4.07 (1.12)	4.15 (1.13)	0.204
Baseline AD severity[f]								
More advanced (baseline MMSE 0–16)								
n	639	331	642	329		488	284	
Value	4.67 (0.80)	4.58 (0.87)	4.31 (1.09)	4.42 (1.10)	0.028	4.29 (1.13)	4.42 (1.11)	0.021
Less impairment (baseline MMSE 17–20)								
n	264	130	265	130		194	111	
Value	3.80 (0.63)	3.88 (0.70)	4.02 (1.01)	3.95 (0.91)	0.595	3.91 (0.99)	3.93 (0.97)	0.921
US population[f]								
n	291	141	292	140		211	120	
Value	4.50 (0.90)	4.45 (0.83)	4.38 (0.97)	4.57 (0.89)	0.033	4.38 (1.01)	4.59 (0.91)	0.051
ADCS-ADL[i]								
n	908	461	908	461		687	400	
Value	34.1 (10.88)	34.5 (11.19)	−1.2 (0.40)	−1.2 (0.45)	0.882	−1.0 (0.48)	−0.9 (0.52)	0.827
MMSE[i]								
n	908	462	908	462		688	398	
Value	13.1 (4.99)	13.1 (4.72)	+0.4 (0.18)	+0.2 (0.20)	0.244	+0.6 (0.22)	+0.3 (0.23)	0.127

ITT = intent-to-treat; LSM = least squares mean; Δ = change from baseline to week 24; LOCF = last observation carried forward; OC = observed cases; SIB = Severe Impairment Battery[21,22]; MMSE = Mini-Mental State Examination[17]; CIBIS+/CIBIC+ = Clinician's Interview-Based Impression of Severity Plus Caregiver Input scale/Clinician's Interview-Based Impression of Change Plus Caregiver Input[26,27]; ADCS-ADL = Alzheimer's Disease Cooperative Study–Activities of Daily Living (severe version).[28]

[a] Patients who received ≥1 dose of study medication and in whom either (1) the SIB total score was available at baseline and ≥1 SIB total score was available after the administration of the first dose of study medication or (2) the CIBIS+ score was available at baseline and ≥1 CIBIC+ overall change score was available after the administration of the first dose of study medication.

[b] The OC population analysis was exploratory for all end points.

[c] Analysis method for the SIB was an ANCOVA model with terms for baseline, country, and treatment for the change from baseline to week 24.

[d] Primary end point.

[e] Preplanned exploratory end point.

[f] Post hoc end point.

[g] For CIBIS+/CIBIC+, values are mean (SD) at week 24 (nonparametric ANCOVA combined with a Cochran-Mantel-Haenszel test, adjusted for CIBIS+ at baseline with a stratification adjustment for country, for CIBIC+ scores at week 24). CIBIS+ scores were collected at baseline and established a point of reference for subsequent CIBIC+ assessments.

[h] Coprimary end point.

[i] Secondary end point. ANCOVA with terms for baseline, country, and treatment for the change from baseline to week 24.

Table IV

Treatment-emergent adverse events* (TEAEs) in patients with moderate to severe Alzheimer's disease who received ≥1 dose of treatment with donepezil 23 or 10 mg/d. Data are number (%) of patients.

Parameter	Donepezil 23 mg/d (n = 963)	Donepezil 10 mg/d (n = 471)
Patients with ≥1 TEAE	710 (73.7)	300 (63.7)
TEAE		
Nausea	114 (11.8)	16 (3.4)
Vomiting	89 (9.2)	12 (2.5)
Diarrhea	80 (8.3)	25 (5.3)
Anorexia	51 (5.3)	8 (1.7)
Dizziness	47 (4.9)	16 (3.4)
Weight decrease	45 (4.7)	12 (2.5)
Urinary tract infection	42 (4.4)	19 (4.0)
Headache	41 (4.3)	15 (3.2)
Fall	39 (4.0)	18 (3.8)
Agitation	38 (3.9)	18 (3.8)
Insomnia	33 (3.4)	11 (2.3)
Bradycardia and sinus bradycardia	27 (2.8)	3 (0.6)
Aggression	26 (2.7)	12 (2.5)
Urinary incontinence	24 (2.5)	6 (1.3)
Fatigue	23 (2.4)	4 (0.8)
Asthenia	20 (2.1)	3 (0.6)
Somnolence	20 (2.1)	5 (1.1)
Contusion	20 (2.1)	1 (0.2)

*_Medical Dictionary for Regulatory Activities_ preferred terms.[32] TEAEs that occurred in ≥2% of patients who received donepezil 23 mg/d and that occurred at a higher frequency with donepezil 23 mg/d than with donepezil 10 mg/d are shown.

Table V

Serious treatment-emergent adverse events* (TEAEs) occurring in ≥0.5% of patients with moderate to severe Alzheimer's disease who received ≥1 dose of treatment with donepezil 23 or 10 mg/d. Data are number (%) of patients.

Parameter	Donepezil 23 mg/d (n = 963)	Donepezil 10 mg/d (n = 471)
Patients with ≥1 serious TEAE	80 (8.3)	45 (9.6)
Serious TEAE		
Fall	6 (0.6)	2 (0.4)
Urinary tract infection	6 (0.6)	2 (0.4)
Pneumonia	3 (0.3)	3 (0.6)
Syncope	2 (0.2)	5 (1.1)
Aggression	2 (0.2)	4 (0.8)
Confusional state	1 (0.1)	3 (0.6)

*Medical Dictionary for Regulatory Activities preferred terms.[32]