Donepezil: a randomised double-blind trial in CADASIL

Martin Dichgans, Hugh S Markus, Stephen Salloway, Auli Verkkoniemi, Margaret Moline, Qin Wang, Holly Posner, Hugues S Chabriat

Summary

Background Cholinergic deficits might contribute to vascular cognitive impairment. Trials of cholinesterase inhibitors in patients with vascular dementia are difficult because of heterogeneous disease mechanisms and overlap between vascular and Alzheimer’s disease (AD) pathology in the age-group recruited. Cerebral autosomal dominant arteriopathy with subcortical infarcts and leucoencephalopathy (CADASIL) is a genetic form of subcortical ischaemic vascular dementia. It represents a homogeneous disease process, and because of CADASIL’s early onset, comorbid AD pathology is rare. We did a multicentre, 18-week, placebo-controlled, double-blind, randomised parallel-group trial to determine whether the cholinesterase inhibitor donepezil improves cognition in patients with CADASIL.

Methods 168 patients with CADASIL (mean age 54·8 years) were assigned to 10 mg donepezil per day (n=86) or placebo (n=82) by a computer-generated randomisation protocol. Inclusion criteria included a mini-mental state examination (MMSE) score of 10–27 or a trail making test (TMT) B time score at least 1·5 SD below the mean, after adjustment for age and education. The primary endpoint was change from baseline in the score on the vascular AD assessment scale cognitive subscale (V-ADAS-cog) at 18 weeks. Secondary endpoints included scores on the ADAS-cog, MMSE, TMT A time and B time, Stroop, executive interview–25 (EXIT25), CLOX, disability assessment for dementia, and sum of boxes of the clinical dementia rating scale. Analysis was done by intention to treat. This trial is registered with ClinicalTrials.gov, number NCT00103948.

Findings 161 patients were analysed. There was no significant difference between donepezil (n=84) and placebo (n=77) in the primary endpoint. The least-squares mean change from baseline score was −0·81 (SE 0·59) in the placebo group and −0·85 (SE 0·57) in the donepezil group (p=0·956). There was a significant treatment effect favouring donepezil on the following secondary outcomes: TMT B time (p=0·023), TMT A time (p=0·015), and EXIT25 (p=0·022). Ten donepezil-treated patients discontinued treatment due to adverse events compared to seven placebo-treated patients.

Interpretation Donepezil had no effect on the primary endpoint, the V-ADAS-cog score in CADASIL patients with cognitive impairment. Improvements were noted on several measures of executive function, but the clinical relevance of these findings is not clear. Our findings may have implications for future trial design in subcortical vascular cognitive impairment.

Funding Eisai Medical Research (Ridgefield Park, NJ, USA).

Introduction Cholinesterase inhibitors provide benefits in cognition, global functioning, and activities of daily living (ADL) in patients with mild to moderate Alzheimer’s disease (AD). By contrast, the efficacy of cholinesterase inhibitors in vascular dementia (VaD) is still disputed.1 Disruption of cholinergic pathways by subcortical ischaemic lesions has provided the rationale for testing cholinergic strategies in VaD.2,3 and indeed, several recent trials have shown a significant benefit of cholinesterase inhibitors on cognition in VaD.4 However, effects on global functioning and ADL have been inconsistent, and regulatory approval for this class of drugs has so far not been granted for use in this condition.

The conduct and interpretation of the results from VaD trials has been difficult for several reasons. First, VaD involves diverse vascular pathologies and dementia mechanisms (eg, strategic infarcts, multiple cortical infarcts, and subcortical ischaemic lesions) that may respond differently to treatment.5–7 Second, the assessment instruments commonly used in clinical trials, such as the AD assessment scale cognitive subscale (ADAS-cog),8 may not be suited for VaD, because these scales were developed for use specifically in AD. Finally, because of the limited specificity of clinical diagnostic criteria for VaD and the high prevalence of AD in elderly people, concurrent AD remains a major concern, and indeed, previous VaD trials have included patients from different diagnostic categories.9–12 Any treatment effect might therefore indicate an effect on coexistent AD. These difficulties have led investigators to suggest doing trials in more narrowly defined subtypes of VaD and to use more specific cognitive scales.13–16 Cerebral autosomal dominant arteriopathy with subcortical infarcts and leucoencephalopathy (CADASIL) is an early onset genetic small-vessel disease that causes lacunar strokes, ischaemic white matter lesions, and subcortical ischaemic vascular dementia.14–16 The clinical
and radiological phenotype of CADASIL closely resembles sporadic small-vessel disease, which accounts for most cases of VaD in the general population.\(^8\) Neuropsychological testing in patients with CADASIL has revealed executive dysfunction as the most prominent cognitive abnormality throughout different disease stages.\(^1,18\) Pronounced deficits are found on processing speed, as assessed, for example, by the trail making test (TMT), and a similar profile of neuropsychological deficits is observed in the more common sporadic forms of subcortical ischaemic vascular dementia.\(^5,17,18\)

This multinational, randomised, double-blind trial was designed to test the hypothesis that donepezil, a potent cholinesterase inhibitor, improves cognition in patients with CADASIL who are cognitively impaired. To account for the profile of cognitive abnormalities in subcortical ischaemic vascular dementia, the trial incorporated secondary measures on executive function and processing speed.

**Methods**

**Participants**

Eligible patients (men and women aged 25–70 years) had a diagnosis of CADASIL documented by a typical mutation in NOTCH3,\(^5\) or by the presence of characteristic electron-dense granular osmiophilic material in blood vessels obtained from biopsy material.\(^19\) All eligible patients had cognitive impairment as defined by both of two criteria: (1) a description of cognitive problems given by patients or their study partners; and (2) a mini-mental state examination (MMSE) score of 10–27 (inclusive),\(^20\) or a TMT B time score 1·5 SDs below the mean, after adjustment for age and education. The decision to include the TMT B time score as an entry criterion was made on the basis of studies showing that CADASIL patients, like those with sporadic small-vessel disease, have deficits on executive function tests with pronounced deficits on timed measures.\(^17,18\) Previous epidemiological studies have shown that patients with CADASIL have exceedingly poor performance on the TMT B time score, despite near normal performance on delayed word recall and word recognition.\(^9,14\) Patients with cardiovascular disease, peripheral artery disease, hypertension, diabetes, or depression were eligible provided these diseases were stable or had been controlled by medication for at least 3 months.

Exclusion criteria were as follows: disorders other than CADASIL that may affect cognition or the ability to assess it; new stroke within the past 12 weeks; clinically relevant conditions affecting absorption, distribution, or metabolism of the study medication; clinically significant, active gastrointestinal, renal, hepatic, respiratory, infectious, endocrine, or cardiovascular system disease; left bundle block; pregnancy; history of chronic alcohol or illegal drug use; known hypersensitivity to cholinesterase inhibitors or piperidine-containing drugs; or unapproved prior or concomitant drugs.

Patients were required to have a reliable study partner who had regular contact with the patient and accompanied the patient at all visits. Before study enrolment, both the caregiver and patient (or legal representative) provided written informed consent to participate. The study was done according to the Declaration of Helsinki and subsequent revisions, and was approved by all institutional review boards.

**Procedures**

This was a multicentre, 18-week, placebo-controlled, double-blind, randomised, parallel-group trial undertaken in 10 countries. Patients were assigned placebo or donepezil by a computer-generated randomisation protocol. Pre-prepared allocation was sent out to centres in advance. Patients in the donepezil group received donepezil 5 mg daily for the first 6 weeks and 10 mg daily thereafter. The randomisation ratio was 1:1.

Psychometric assessments, physical and neurological examinations, measurements of vital signs, and laboratory investigations were done at screening, baseline, and (together with assessments for medication compliance and adverse events) at weeks 6, 12, and 18. In addition, patients received the Montgomery-Asberg...
depression rating scale at screening, and the US National Institutes of Health stroke scale, the modified Rankin scale, and the Hachinski ischaemia scale at baseline.

Patients were required to have a recent (within 6 months) cranial MRI consistent with CADASIL, which was done for study purposes if not already available. Patients in whom an MRI was contraindicated had a CT scan. Brain MRI was done in all but 16 of the randomised patients at screening. Patients were not permitted to receive anticholinergic drugs or cholinergic agents other than donepezil during the study period.

The primary efficacy measure was the vascular ADAS-cog (V-ADAS-cog), which includes the ADAS-cog and a number cancellation and maze test. The ADAS-cog is a composite of individual and independently valid measures, many of which have been rescaled. The V-ADAS-cog was composed with the addition of two of the three scales recommended by Mohs and colleagues to broaden the scope of the ADAS-cog. The maze and the number cancellation tasks were chosen to better assess the characteristic attentional and executive dysfunction found in VaD, and were both rescaled to give a total composite V-ADAS-cog score. The number cancellation task was rescaled to cover a 5-point spread, and the maze test was rescaled to give a score 0 for a perfect maze and 5 for anything less than perfect.

Secondary efficacy measures were ADAS-cog, MMSE, and the following executive function tests: TMT part A and part B time, which scores the time needed to complete a specific task; executive interview-25 (EXIT25), a 25-item interview scored from 0 to 50; Stroop colour and word test; and CLOX, an executive clock-drawing test. Additional secondary efficacy measures included the disability assessment for dementia (DAD) scale, which assesses the patient’s ability to do basic ADL and instrumental ADL (IADL), and the sum of boxes of the clinical dementia rating (CDR) scale (CDR-SB), a multidimensional scale for dementia severity.

Safety and tolerability were assessed by comparing the proportions of treatment-emergent adverse events and discontinuation between treatment groups, as well as changes from baseline in laboratory test results, vital signs, EKG abnormalities, and physical examination.
The power of this study was calculated based on the last observation carried forward (LOCF) analysis. To analyse TMT in the ITT population, the primary analysis was an intention-to-treat (ITT) population analysis at week 18 with last observation carried forward (LOCF). The ITT LOCF population included all patients who had received at least one dose of study medication, had a baseline assessment, and had at least one post-baseline assessment for which the last post-baseline observation for each patient was used. The main comparison of donepezil versus placebo for the primary efficacy endpoint—change from baseline to week 18 LOCF in the V-ADAS-cog score—was assessed by use of an analysis of covariance (ANCOVA) model with terms for baseline score, treatment, and pooled centres (see Study investigators section for details). Treatment comparisons of changes from baseline at each visit (observed cases) for the primary endpoint were analysed in a similar manner. The least squares of means estimated from ANCOVA model for change from baseline to week 18 LOCF in the V-ADAS-cog score—were reported by use of frequency calculations and descriptive statistics. All analyses were done using SAS version 8.1.

### Role of the funding source

The sponsor, Eisai Medical Research (Ridgefield Park, NJ, USA), was responsible for operational aspects of the trial, including data collection, data storage, and data analysis, according to the approved study and statistical analysis plans. The sponsor had no role in writing the manuscript, except for editing, and had no role in the decision to submit it for publication. The study was independently monitored by Parexel (Waltham, MA, USA). The academic authors had unrestricted access to the derived dataset, and assume full responsibility for the completeness, integrity, and interpretation of the data as well as writing of the study report and the decision to submit for publication.

### Results

The trial was done between Jan 13, 2005, and Oct 20, 2006. Of the 267 patients screened, 168 were enrolled and randomly assigned to receive placebo (n=82) or donepezil (n=86; figure 1). Reasons for screening failure are shown in figure 1. Patients were enrolled in Europe (n=133, 79%), the USA (n=26, 15%), and Canada (n=9, 5%; see Study investigators section for details).

The two treatment groups were well balanced in terms of baseline demographics, medical history, clinical characteristics, and baseline psychometric scores (table I). All patients had multiple subcortical lesions on brain MRI, and two patients had territorial infarctions. 33 (20%) patients were demented as defined by a global CDR score of at least 1 plus an MMSE score of 26 or lower. 52 (31%) patients had an MMSE score of 26 or lower, and 109 (81%) had an abnormal TMT B score. 109 (65%) patients reported a gradual onset of cognitive impairment (sudden onset in 58 [35%]), and 96 (57%) had shown an insidious,

### Statistical analysis

The power of this study was calculated based on the primary endpoint, change from baseline in V-ADAS-cog, and a review of the results of phase III trials of donepezil in patients with VaD. The two-sided t test with a significance level of 5% was used, and the SD was assumed to be 5 for the change from baseline in V-ADAS-cog. On the basis of an anticipated total of 148 patients providing efficacy data, this study had 80% power to detect a difference in V-ADAS-cog change from baseline means of 2.45.

For the efficacy analysis, the primary analysis was an intention-to-treat (ITT) population analysis at week 18 with last observation carried forward (LOCF). The ITT LOCF population included all patients who were randomised, had received at least one dose of study medication, had a baseline assessment, and had at least one post-baseline assessment for which the last post-baseline observation for each patient was used. The main comparison of donepezil versus placebo for the primary efficacy endpoint—change from baseline to week 18 LOCF in the V-ADAS-cog score—was assessed by use of an analysis of covariance (ANCOVA) model with terms for baseline score, treatment, and pooled centres (see Study investigators section for details). Treatment comparisons of changes from baseline at each visit (observed cases) for the primary endpoint were analysed in a similar manner. The least squares of means estimated from ANCOVA model for change from baseline to week 18 LOCF in the V-ADAS-cog score—were reported by use of frequency calculations and descriptive statistics. All analyses were done using SAS version 8.1.

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constant decline before the study (stepwise or fluctuating in 72 [43%]).

Study completion was 89% in the placebo group and 85% in the donepezil group. Most discontinuations were due to adverse events. Two patients, one assigned to placebo and one assigned to donepezil, withdrew consent. The mean overall compliance with study medication was 94% in the placebo group and 95% in the donepezil group. The mean daily donepezil dose in the treatment group (n=86) was 8·24 mg (SE 0·31).

Concomitant drugs were common (table 1). The most frequently taken drug classes were antithrombotic drugs, lipid-reducing drugs, antihypertensive drugs that affect the renin-angiotensin system, β-blockers, and calcium-channel blockers. Additional classes included antidepressants, anxiolytics, antipsychotics, and antiepileptics.

There was no significant difference in the V-ADAS-cog change from baseline in the LOCF (primary) analysis of the ITT population at 18 weeks between patients assigned donepezil and those assigned placebo (table 2). Both groups showed slight improvement on the V-ADAS-cog at week 18 LOCF compared to baseline. The least-squares mean change from baseline score was –0·81 (SE 0·59) in the placebo group and –0·85 (SE 0·57) in the donepezil group. Confirming the LOCF analysis, there were no significant differences in the observed-cases analyses of the ITT population at weeks 6, 12, and 18 between patients assigned donepezil and those assigned placebo (figure 2).

For broad cognitive assessments included in the secondary efficacy measures, LOCF analysis of the ITT population at week 18 showed no differences on the ADAS-cog and the MMSE between the two groups (table 2). On the executive function tests in pre-specified analyses, patients treated with donepezil showed significantly greater improvements on TMT A time, TMT B time, and EXIT25 (tables 2 and 3).

The least-squares mean change analysis on the TMT B time yielded a significant treatment effect at week 18 LOCF (p=0·005; table 3). However, 39 patients in the ITT population were unable to complete the TMT B test at baseline (20 placebo, 19 donepezil), whereas 40 patients were unable to complete the test at week 18 follow-up visits (23 placebo, 17 donepezil). Thus, a notable number of ITT patients were excluded from this analysis (table 3, figure 2). In the subset of patients who completed the test both at baseline and at study endpoint, baseline TMT A time differed between the placebo (least-squares mean 74·15 s [SE 4·58]) and donepezil group (59·59 s [SE 4·48]; p=0·019). A baseline difference was also observed between the two treatment groups who completed the TMT B test (placebo 138·84 s [SE 8·44], donepezil 116·94 s [SE 8·10]; p=0·048). The baseline scores were used as covariates in the least-squares mean change analysis.

To account for the limitations of the least-squares mean change analysis of the TMT we also did time-to-event analyses (log-rank tests), which included censored times from patients unable to complete the test (figure 3).

Baseline values of TMT A and B did not differ significantly between treatment groups (table 1). Confirming the results of the least-squares mean change analysis, there
was a significant difference between the two treatment groups that favoured donepezil over placebo at week 18 LOCF (p=0.023) but not at baseline (p=0.229). Data from all 168 randomised patients are included.

Table 3: Trail making test (TMT) results in placebo-treated and donepezil-treated patients at week 18 (LOCF analysis)

<table>
<thead>
<tr>
<th></th>
<th>Placebo</th>
<th>Donepezil</th>
<th>Difference (95% CI)</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Subset of patients who completed the TMT test at baseline and endpoint</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Part A time</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Number of patients</td>
<td>74</td>
<td>78</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Least-squares mean (SE) change from baseline score</td>
<td>-3.10 (2.34)</td>
<td>-11.15 (2.28)</td>
<td>-8.05 (-14.31 to -1.79)</td>
<td>0.012</td>
</tr>
<tr>
<td>Part B time</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Number of patients</td>
<td>48</td>
<td>54</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Least-squares mean (SE) change from baseline score</td>
<td>-8.87 (6.21)</td>
<td>-32.21 (6.02)</td>
<td>-23.34 (-39.60 to -7.08)</td>
<td>0.005</td>
</tr>
<tr>
<td><strong>ITT population (time-to-event analysis)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Part A time</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Number of patients</td>
<td>76</td>
<td>82</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Median (range) time (s)</td>
<td>60 (15–300)</td>
<td>43 (17–300)</td>
<td></td>
<td>0.015†</td>
</tr>
<tr>
<td>Number (%) of patients who did not complete the test within 300 s</td>
<td>1 (1.3%)</td>
<td>1 (1.2%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Part B time</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Number of patients</td>
<td>74</td>
<td>78</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Median (range) time (s)</td>
<td>166 (37–300)</td>
<td>105 (33–300)</td>
<td></td>
<td>0.023†</td>
</tr>
<tr>
<td>Number (%) of patients who did not complete the test within 300 s</td>
<td>23 (31.1%)</td>
<td>17 (21.8%)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*Negative changes indicate improvement. †Log-rank test.

Figure 3: Time-to-event analysis for the time needed to complete TMT B time at week 18 LOCF

There was a significant difference between the two treatment groups favouring donepezil over placebo at week 18 LOCF (p=0.015 for TMT A; p=0.023 for TMT B; table 3). The median time to complete the TMT B test was 105 s in the donepezil-treated patients and 166 s in the placebo-treated patients (table 3). The proportion of donepezil-treated patients who completed the test at week 18 LOCF was greater than at baseline (78% vs 75%), whereas the proportion of placebo-treated patients who completed the test at week 18 LOCF was smaller than at baseline (69% vs 73%; figure 3).

Results on the EXIT25 at week 18 in observed cases showed a least-squares mean change from baseline score of -0.11 (SE 0.51) in the placebo group (LOCF: 0.14 [SE 0.48]) and -1.55 (SE 0.53) in the donepezil group (LOCF: -1.33 [SE 0.47]; both p=0.02; table 2). Mean improvements in CLOX1 and CLOX2 were greater in patients assigned donepezil than in patients assigned placebo, although not significantly (table 2). No significant differences between the treatment groups were found on the Stroop test.

Analysis of DAD scores for IADL showed no significant functional effects of donepezil treatment at week 18 LOCF (table 2). In both treatment groups, DAD scores remained close to baseline with numerical improvements at weeks 6, 12, and 18 for observed cases, and week 18 LOCF (figure 2). Results on the CDR-SB at week 18 LOCF showed no treatment effect of donepezil on overall dementia levels (table 2).

To check for a possible influence of baseline cognition on the therapeutic response, additional analyses were done. Subgroup analyses in patients with a baseline MMSE score of 26 or lower (25 placebo; 27 donepezil) and in patients with a baseline MMSE score above 26 (51 placebo; 55 donepezil) revealed no significant treatment effect on the V-ADAS-cog in either subgroup (both p>0.5). Similar subgroup analyses on the TMT A and B time showed a significant treatment effect in patients with a baseline MMSE score above 26. For TMT B time, both the least-squares mean change and time-to-event analyses yielded a significant result (41 placebo, 46 donepezil for least-squares mean change; and 51 placebo, 55 donepezil for time to event; p=0.004). No significant treatment effect on the TMT B time was found in patients with a baseline
MMSE score below 26. However, only a few patients within this group completed the test at baseline and post-baseline for the least-squares mean change analysis, whereas all patients in each treatment group were included in the time-to-event analysis.

The proportion of patients with treatment-emergent adverse events was higher in the donepezil group than in the placebo group (81% vs 71%; table 4). The adverse events that occurred in more than 5% of donepezil-treated patients corresponded to the known spectrum of adverse events associated with cholinesterase inhibitors. Generally, adverse events were mild to moderate, and resolved without the need to discontinue study medication. The percentage of patients who cited adverse events as a reason for discontinuation was similar in both groups, with the exception of nausea (donepezil 5%, placebo 0%) and vomiting (donepezil 3%, placebo 0%).

Serious adverse events other than death were reported in nine (11%) patients assigned to placebo and in 15 (17%) patients assigned to donepezil. There was only one death, which occurred in a patient from the placebo group due to cardiac failure; this was considered to be unrelated to the study drug.

Discussion
This double-blind, multinational, randomised study was designed to determine the efficacy of the cholinesterase inhibitor donepezil in CADASIL, a model of pure subcortical ischaemic vascular dementia. Donepezil resulted in no improvement in the primary endpoint, cognition assessed by the V-ADAS-cog. However, improvements were detected in several prespecified secondary endpoints, which deserve some attention.

This trial used a novel design, which took into account many of the limitations of previous VaD trials. First, by contrast with all previous trials, it focused on a specific subtype of vascular cognitive impairment: small-vessel disease. Second, previous VaD trials have included elderly (mean age ~75 years) patients with possible or probable VaD. This group is likely to have substantial coexistent AD pathology. To overcome this limitation, we studied patients with the genetic form of small-vessel disease, and excluded patients older than 70 years. Third, this study applied dedicated cognitive scales for VaD, including executive function tests.

Despite careful study design, there was no significant treatment effect of donepezil on cognition as assessed by the primary endpoint, V-ADAS-cog, and by ADAS-cog and MMSE. These tests assess a broad range of cognitive functions. The absence of a treatment effect may represent a true lack of efficacy of cholinesterase inhibitors in this group of patients, although several factors might have made it difficult to detect a true treatment effect on broad cognitive assessments. First, by including patients with mild cognitive impairment, this study might have encountered a ceiling effect for the V-ADAS-cog, ADAS-cog, and MMSE. Interestingly, however, patients with poorer baseline cognition (MMSE score ≤26) likewise failed to show a treatment effect in subgroup analyses. In fact, there was not even a trend for a treatment effect in the more severely affected cases (data not shown). Second, as was expected from the known natural history of CADASIL, the placebo group did not deteriorate during the trial. This means that an actual treatment effect would have required a true improvement in the active group, which is more challenging to achieve. However, the results from previous VaD trials show that detecting improvements on the ADAS-cog against a stable placebo group is possible. Third, the trial duration was fairly short (18 weeks) and was shorter than in previous donepezil VaD trials. However, these trials found no additional benefit of donepezil at week 24 compared to week 18. Fourth, the study sample was fairly small. However, the trial was sufficiently powered to detect a treatment effect in the range of previous VaD trials, which was definitely not found.

<table>
<thead>
<tr>
<th>Adverse events affecting &gt;5% of donepezil-treated patients and at least double that in placebo group</th>
<th>Placebo (n=82)</th>
<th>Donepezil (n=86)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Any adverse events</td>
<td>58 (71%)</td>
<td>70 (81%)</td>
</tr>
<tr>
<td>Gastrointestinal system</td>
<td>14 (17%)</td>
<td>34 (40%)</td>
</tr>
<tr>
<td>Nausea</td>
<td>3 (4%)</td>
<td>16 (19%)</td>
</tr>
<tr>
<td>Diarrhoea</td>
<td>3 (4%)</td>
<td>13 (15%)</td>
</tr>
<tr>
<td>Vomiting</td>
<td>1 (1%)</td>
<td>10 (12%)</td>
</tr>
<tr>
<td>Musculoskeletal and connective tissue</td>
<td>11 (13%)</td>
<td>15 (17%)</td>
</tr>
<tr>
<td>Muscle cramps</td>
<td>0</td>
<td>6 (7%)</td>
</tr>
<tr>
<td>Nervous system</td>
<td>28 (34%)</td>
<td>33 (38%)</td>
</tr>
<tr>
<td>Dizziness</td>
<td>1 (1%)</td>
<td>5 (6%)</td>
</tr>
<tr>
<td>Psychiatric disorder</td>
<td>9 (11%)</td>
<td>23 (27%)</td>
</tr>
<tr>
<td>Insomnia</td>
<td>2 (2%)</td>
<td>5 (6%)</td>
</tr>
<tr>
<td>Possibly drug-related adverse events</td>
<td>28 (34%)</td>
<td>52 (60%)</td>
</tr>
<tr>
<td>Adverse events resulting in treatment discontinuation</td>
<td>7 (9%)</td>
<td>10 (12%)</td>
</tr>
<tr>
<td>Adverse events affecting the cerebrovascular system</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ischaemic stroke</td>
<td>3 (4%)</td>
<td>5 (6%)</td>
</tr>
<tr>
<td>Transient ischaemic attack</td>
<td>7 (9%)</td>
<td>1 (1%)</td>
</tr>
<tr>
<td>Serious adverse events affecting &gt;2% of patients in either group</td>
<td></td>
<td></td>
</tr>
<tr>
<td>At least one serious adverse event</td>
<td>9 (11%)</td>
<td>15 (17%)</td>
</tr>
<tr>
<td>Gastrointestinal disorders</td>
<td>2 (2%)</td>
<td>1 (1%)</td>
</tr>
<tr>
<td>General disorders and administration site conditions</td>
<td>0</td>
<td>2 (2%)</td>
</tr>
<tr>
<td>Neoplasms</td>
<td>2 (2%)</td>
<td>0</td>
</tr>
<tr>
<td>Nervous system disorder</td>
<td>6 (7%)</td>
<td>11 (13%)</td>
</tr>
<tr>
<td>Ischaemic stroke</td>
<td>2 (2%)</td>
<td>4 (5%)</td>
</tr>
<tr>
<td>Transient ischaemic attack</td>
<td>3 (4%)</td>
<td>1 (1%)</td>
</tr>
<tr>
<td>Epilepsy</td>
<td>0</td>
<td>2 (2%)</td>
</tr>
<tr>
<td>Psychiatric disorders</td>
<td>0</td>
<td>2 (2%)</td>
</tr>
<tr>
<td>Death</td>
<td>1 (1%)</td>
<td>0</td>
</tr>
</tbody>
</table>

Data are numbers (%). *Adverse events defined as possibly trial-drug related include those thought possible, probable, and very likely.

Table 4: Treatment-emergent adverse events
Of interest, this trial showed a significant benefit in favour of donepezil on several measures of executive function and processing speed. The most prominent effect was seen on the timed measure of the TMT B. Several observations suggest that this effect is real. First, the results of the prespecified least-squares mean change analysis are confirmed by a time-to-event analysis for the time needed to complete the test. This analysis uses all available data, including censored times from patients unable to complete the test within 300 s. Indeed, about one-third of patients randomised were not able to complete the TMT B within 300 s and, apart from a beneficial effect in the time-to-event analysis, donepezil treatment also had a beneficial effect on the proportion of completers (figure 3). Second, the beneficial effect of donepezil was seen against a slight improvement in the placebo group. Again, one would expect that this would have made it more difficult to show a significant treatment effect, which was nevertheless observed. Third, a similar treatment response was also seen on other executive tests, including the timed measure of the TMT A and EXIT25.

The beneficial effect of donepezil on the TMT B and other executive tests is of great interest because it emphasises an involvement of cholinergic deficits in executive dysfunction.68 One of the major networks implicated in executive control is the dorsolateral prefrontal-subcortical circuit.51 This network connects the dorsolateral prefrontal cortex with subcortical and other cortical areas, and has been shown to be affected by subcortical ischaemic lesions.4,5,11,13 Like other cortical areas, the prefrontal cortex is densely innervated by cholinergic projections from the nucleus basalis of Meynert. These projections radiate through the cerebral white matter,4,14 and histopathological studies have shown a loss of cortical and subcortical cholinergic fibres in CADASIL patients and in patients with sporadic small-vessel disease.4,14,15 Thus, there is an anatomical and pathophysiological basis to explain the beneficial effects of cholinesterase inhibitors in this disease.

This trial illustrates the limitations of the ADAS-cog, and the need to use executive function tests as outcome measures in future interventional trials.5 By contrast with AD, VaD is associated with prominent deficits on executive tasks. This is particularly pronounced in patients with small-vessel disease and subcortical ischaemic lesions.4,7,8 Nevertheless, previous VaD trials have focused on the ADAS-cog, which has been developed for use in AD, and few trials have included tests on executive function.11,12 Attempts to broaden the scope of the ADAS-cog have resulted in several extended versions of this test.13,14 Our study suggest that these instruments need to be developed further and that measures of processing speed such as the TMT B should be included in future interventional trials.

Despite a beneficial effect on executive function tests, donepezil showed no treatment effects on IADL and global dementia rating as assessed by the DAD and CDR-SB, respectively. This might indicate that the improvements on executive scores do not translate into a clinically meaningful benefit. However, the IADL scores in the placebo group remained stable and improvements on IADL are known to be particularly difficult to achieve.8,31 This is partly because IADL is influenced by multiple factors, including sensorimotor deficits, that were present in the current sample but are unlikely to improve from cognitive therapy.

The type and incidence of adverse events were consistent with the known safety profile of donepezil and were similar to those reported in the VaD trials, except for a lower incidence of cardiovascular adverse events, which was expected in the current population.

In summary, this study found no significant treatment effect of donepezil on cognition as assessed by the primary efficacy measure, V-ADAS-cog. Improvements were noted on several measures of executive function, but the clinical relevance of this finding is not clear. The results emphasise the importance of focusing on aetiological subgroups of vascular cognitive impairment and of using dedicated neuropsychological tests that cover the characteristic profile of cognitive abnormalities in vascular cognitive impairment. CADASIL seems suited to explore novel therapeutic approaches for vascular cognitive impairment and subcortical dementia.

Contributors
MD and HC were the co-principal investigators of the study. MD, HSM, SS, HP, and HC participated in the planning and execution of the study, and contributed to the development of the study report. HP and MM were responsible for the overall planning and conduct of the study for the sponsor. QW was responsible for the statistical analysis. MD wrote the first draft of the manuscript with additional input from HSM and HC. MD supervised subsequent revisions based on critical comments from all authors. All authors have seen and approved the final version of the manuscript.

Study investigators
Canada—Vladimir Hachinski, Ocean Ozdemir, Silva DiLegge, Dinesh Kalra (The London Health Services Center, London, ON; 5 patients); Michael Hill, Vanessa Palumbo (Departments of Clinical Neurosciences, Medicine, and Community Health Sciences, University of Calgary, Calgary, AB; 4 patients). Finland—Auli Verkkoniemi (Department of Clinical Neurosciences, Helsinki University Central Hospital, Helsinki; 17 patients); Seppo Tuisku (Department of Neurology, University Hospital, Turku; 4 patients). France—Hugues Chabriat, Marie-Germaine Bousser, Katayoun Vahedi, Christian Stapf, Anand Viswanathan, Aline Mourad, Sonia Reyes (neuropsychologist), Annie Kurtz (neuropsychologist; Department of Neurology, Lariboisière Hospital, Denis Diderot University Paris VII, Paris; 28 patients). Germany—Martin Dichgans, Andreas Kochwendtner, Yonne Mewald, Christian Opherk, Nils Peters (Department of Neurology, Grosshadern Hospital, Denis Diderot University Paris VII, Paris; 28 patients). Italy—Leonardo Pannoni, Cristina Sarti (Department of Neurology and Psychiatric Sciences, University of Florence, Florence; 8 patients); Antonio Federico, Maria Dotti, Maria Laura Stromillo, Monica De Santis (Department of Neurological and Behavioural Sciences, University of Siena, Siena; 7 patients). Sweden—Andreas Terent, Anna Stenborg (Department of Medical Sciences, Uppsala University and University Hospital, Uppsala; 4 patients). Switzerland—Hansjörg Hungerbühler, Karen Wachter (Neurological Clinic, Kantonsspital Aarau AG, Aarau; 3 patients),Spain—Enolpio Gil Néciga, Ilgu Rojas Mazcos (Service of Neurology, Virgen Del Rocio Hospital, Seville; 7 patients). UK—Hugh S Markus, Kristin Hannesdottir (Centre for Clinical...
Neurology, St George's, University of London, London; 16 patients); Keith Muir, Saif Razvi (Division of Clinical Neurosciences, University of Glasgow, Glasgow; 2 patients). USA—Stephen Salloway, Paul Malloy (Memory and Aging Program, Butler Hospital, Providence, RI; 11 patients); James W Schmidek (Department of Neurology, University of Arkansas for the Medical Sciences, Little Rock, AR; 1 patient); Edwin H Koldony, Gregory Pastores (Department of Neurology, New York University School of Medicine, New York, NY; 6 patients); Michael Geschwind, Bruce Miller, Joel Kramer (Department of Neurology, Memory and Aging Center, University of California, San Francisco Medical Center, San Francisco, CA; 3 patients); Jose Biller (Department of Neurology, Loyola University Medical Center, Stritch School of Medicine, Maywood, IL; 3 patients). For the analyses, the 18 study centres were pooled for country, with the exception of the three centres from Switzerland, Sweden, and Spain, which were pooled together.

Conflicts of interest
MD, HSD, SS, and HC participated as investigators and received consultancy fees from Eisai Medical Research (Ridgefield Park, NJ, USA). MD received a research grant support from Eisai Medical Research Inc. MM and QW are employees of Eisai Medical Research. HP was an employee of Eisai Medical Research until August, 2007, and has been an employee of Pfizer since September, 2007.

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References


